BULLETIN

OF

THE JOHNS HOPKINS HOSPITAL

(THE PUBLICATION OF THE MEDICAL SCHOOL AND HOSPITAL)

Vol. XXXIII—No. 372] BALTIMORE, FEBRUARY, 1922 [Price, 50 Cents

CONTENTS

	PAGE
Immunological Reactions of Bence-Jones Proteins. I. Differences Between Bence-Jones Proteins and Human Serum Proteins. (Illustrated.) By S. Bayne-Jones and D. Wright Wilson	37
Yaws. An Analysis of 1046 Cases in the Dominican Republic. (Illustrated.) By W. L. Moss and G. H. Bigelow	43
Studies on a Case of Chromic Acid Nephritis. (Illustrated.) By Ralph H. Major	56
Adaptation of Bacteria to Growth on Human Mucous Membranes with Special Reference to the Throat Flora of Infants. By Arthur L. Bloomfield	61
Dermoid Cysts of the Ovary. A Report of Four Cases. (Illustrated.) By Karl H. Martzloff	66
Titles of Papers Appearing During the Year 1921, Elsewhere than in the Bulletin, by the Present and Former Members of The Johns Hopkins Hospital and Medical School Staff	69

Entered as Second-Class Matter at the Baltimore, Maryland, Postoffice
Acceptance for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917. Authorized on July 3, 1918.

IMMUNOLOGICAL REACTIONS OF BENCE-JONES PROTEINS

I. DIFFERENCES BETWEEN BENCE-JONES PROTEINS AND HUMAN SERUM PROTEINS

By S. Bayne-Jones and D. Wright Wilson

(From the Department of Pathology and Bacteriology and of Physiological Chemistry, The Johns Hopkins University, Baltimore)

In a previous paper,[1] presenting a preliminary account of our study of the immunological reactions of Bence-Jones proteins, we have reported that by the use of the precipitin, complement-fixation and anaphylactic reactions we have been able to show that differences exist between the so-called Bence-Jones protein and the proteins of human serum, and also between preparations of Bence-Jones protein from various sources. While the specimens of Bence-Jones protein which we studied were all typical as regards their phases of coagulation and solution by heat in an acid medium, they differed considerably in their physical properties and in their immunological reactions. These differences were indeed so great that we were forced to regard the so-called "Bence-Jones body" as a group of similar, but not identical, substances, and to refer to the group as the Bence-Jones proteins. One of these proteins (No. 4) crystallized spontaneously in the urine of the patient who excreted it. This property permitted purification of the substance by recrystallization. An account of this patient (R) with a description of the protein has been published by Walters[2] from the Mayo Clinic, where the patient was under observation on the service of Dr. Rowntree. The other specimens of Bence-Jones proteins used by us were isolated from urine by various methods of precipitation. They will be described in detail in our paper dealing with their specific immunological differences. In the present report, we shall give the evidence in support of the contention that it is possible by the use of immunological methods to differentiate Bence-Jones proteins from the proteins of human serum.

With the more frequent use of purified proteins in immunological studies, an increasing number of them are being found to possess individual antigenic specificity. It has been known for a long time that the proteins of the lens of the eye and of spermatozoa have this characteristic, and more recently Wells and Osborne,[3] using purified vegetable proteins, Woods[4] using the pigment from the uveal tract, and Dale and Dakin[5] with crystalline albumin from the eggs of hen and duck, have established the fact that chemical composition, rather than biological origin, is the basis of the specificity of these substances. The chemical and physical peculiarities of Bence-Jones proteins and their absence from the blood and urine of normal persons have conveyed the obvious suggestion that it might be possible by immunological studies to draw a distinction between the blood-proteins and Bence-Jones proteins. This phase of the question has occupied the attention of a number of investi-

gators. The results, however, of the experiments of all except two students of this problem have been reported as indicative of an identity rather than a difference between these proteins.[6, 7, 8, 9] From accounts of the way in which the experiments were conducted, and from the results of our work, it seems that the uncritical use of mixtures of proteins has led to these equivocal results. The most notorious example of this is the work of Abderhalden and Rostoski,[6] which has influenced many of the subsequent immunological studies of Bence-Jones proteins and the opinions upon the nature of Bence-Jones proteinuria. The patient studied by Abderhalden had chronic nephritis as well as multiple myelomata. As a consequence of the two diseases he excreted in his urine Bence-Jones protein and proteins which Cameron and Wells,[10] in studies of the urine in nephritis, have shown to be identical with the proteins of human serum. Abderhalden injected the whole urine of this patient into a rabbit, and obtained an immune serum which precipitated both Bence-Jones protein and human serum. In drawing his conclusions, however, he neglected the possibility that he was dealing with a mixture, and developed his ideas about the identity of Bence-Jones protein and serum proteins as if he had been using single pure antigens. It now seems probable that unless a Bence-Jones protein can be separated from urine by crystallization, and purified by recrystallization, it is impossible to separate it by any method of fractional precipitation from other proteins which are usually present with it in the urine.

The investigators who have succeeded in finding immunological differences between Bence-Jones proteins and serum proteins are Massini [11] and Hektoen.[12] By means of the complement-fixation test, Massini was able to show that an antiserum to the preparation used by him fixed complement in the presence of higher dilutions of the Bence-Jones protein than of human serum. Hektoen's recently published preliminary note reports that by absorption of precipitins specific reactions can be obtained which sharply differentiate Bence-Jones proteins from the proteins of human serum, even when mixed antigens are used.

Reports of Experiments

In our experiments to discover, if possible, immunological differences between Bence-Jones proteins and the proteins of human serum, we used precipitin and complement-fixation reactions with the sera of rabbits immunized to human serum and to several preparations of Bence-Jones proteins, and anaphylactic reactions of guinea-pigs sensitized to these substances.

Precipitin Reactions

The precipitin-sera were prepared as follows:

Anti-human serum. Rabbit No. 161 immunized to human serum by 7 intravenous injections at intervals of 2 to 6 days. The first dose was 0.5 c. c., the last 12 c. c. of serum. Ten days after the last injection, the animal was bled, when its serum gave a precipitate with a 1-1000 dilution of human serum.

Anti-Bence-Jones protein sera: Rabbit No. 144 was immunized to the crystalline Bence-Jones protein (No. 4) by six intravenous injections of a 1 per cent solution of No. 4 at intervals of 4 to 6 days. The first dose was 2 c. c., the last 20 c. c. Ten days after the last injection, when the rabbit's serum caused a precipitate in a 1-1,000,000 dilution of a 4 per cent solution of No. 4, the animal was bled.

Rabbit No. 153 was injected intravenously at intervals of 4 to 6 days with amounts of a 0.5 per cent solution of Dr. J. Rosenbloom's preparation of Bence-Jones protein increasing from 3 c. c. to 20 c. c. Six days after the fifth injection, the rabbit was bled. Precipitin titer 1-100,000 (antigen dilution).

Rabbit No. 189 was immunized to a preparation of Bence-Jones protein designated as "Simpson," given us by Dr. C. G. Guthrie. After 8 injections of amounts of 2-6 c. c. of a 2 per cent solution of this protein, at intervals of 3 to 5 days, the precipitin titer of this animal was 1-2000 (antigen dilution).

Rabbit No. 195 was immunized to a preparation of Bence-Jones protein denoted as "Farrel," and given to us by Dr. C. G. Guthrie. At intervals of six days, 1 c. c., 5 c. c., and 7 c. c. of a 3 per cent solution of this protein were injected intravenously. Five days after the last injection, when the animal was bled, the titer of the serum was 1-8000 (antigen dilution).

With the exception of No. 4, which was the crystalline Bence-Jones protein, the other Bence-Jones proteins were non-crystalline, and had been isolated from urine by various methods of precipitation.

TABLE I

Precipitin Reactions

Antihuman serum 161. Precipitation with antigen	Dilution of antigen			
	0	1-10	1-100	1-1000
Human serum	++++	+++	++	+
Bence-Jones protein (4 per cent solution).	.....	.....	.....	.....
No. 4 (crystalline)	0	0	0	0
No. 1	+	0	0	0
Coag. No. 2	0	0	0	0
Coag. R. urine	+	0	0	0
R. urine	++	+	0	0
Taylor	++	+	0	0
Farrel	++	+	+	0
Simpson (2 per cent)	0	+	++	0
Dine	+	+	0	0
Dine urine	+	++	+	0
X	++	+	0	0
X urine	+++	++	+	0
Rosenbloom	+	+	0	0

The precipitin tests were done in clean sterile tubes, with clear solutions of the sera and antigens. False results due to bacterial growth were eliminated. The antigens, in various dilutions, were layered upon the anti-sera, and the first reading was made by noting the presence or absence of precipitate at the plane of junction of the two fluids one hour after their apposition. The fluids were then mixed, placed in the incu-

bator at 37° C. for 24 hours, and a second reading taken of the sediment in the bottom of the tubes. The controls, which are omitted from the following tables, were made by mixing equal amounts of each component with normal salt solution and incubating these mixtures with the series of tests. When precipitate occurred in the controls, the corresponding tests were discarded or repeated with fresh solutions. In the tables, the signs indicate the amount of precipitate formed; O denoting no precipitate, ++++ a very heavy precipitate. The results of the precipitin reactions with antihuman serum are summarized in Table I.

The advantage gained from the use of a pure crystalline protein is at once apparent from the data presented in Table I. The antiserum to human serum proteins does not precipitate the crystalline preparation of Bence-Jones protein. On the other hand, antihuman serum forms a precipitate with all non-crystalline Bence-Jones proteins which have been salted-out

TABLE II

PRECIPITIN REACTIONS

Serum	Precipitation with	Dilution of antigen					
		0	1-10	1-100	1-1000	1-2000	1-100,000
144. Anti-Bence-Jones, No. 4.	Bence-Jones, No. 4 (4 per cent).	0	+	+++	++++	++++	+++
	Human serum...	0	0	0	0	0	0
159. Anti-Bence-Jones, Rosenbloom.	Bence-Jones, Rosenbloom (4 per cent).	0	+	++	+++	+++	+
	Human serum...	0	+	++	+++	+	0
189. Anti-Bence-Jones, Simpson.	Bence-Jones, Simpson (2 per cent).	++++	++++	+++	++	+	0
	Human serum...	++	+	0	0	0	0
195. Anti-Bence-Jones, Farrel.	Bence-Jones, Farrel (4 per cent).	++++	++++	+++	++	++	0
	Human serum...	+	++	+	0	0	0

or otherwise precipitated from urine. With the whole urine from patients with multiple myelomata, containing presumably more protein identical with the proteins of serum, the precipitation by antihuman serum is greater than with the fractions of these urines containing the Bence-Jones protein.

In Table II are summaries of precipitin reactions with human serum, antisera to several preparations of Bence-Jones proteins and their homologous antigens.

From Table II it is seen that a very potent antiserum to the crystalline Bence-Jones protein does not precipitate human serum, while the antisera to the other less pure preparations of Bence-Jones proteins give "cross-reactions," precipitating both their homologous antigens and human serum.

As Hektoen [12] has pointed out, the method of absorption of precipitins can be used, when mixtures of proteins are unavoidable, to demonstrate differences between serum proteins and Bence-Jones proteins. There is, however, much to be learned about this method before the results obtained with it can be correctly interpreted.[13, 14] In its use, we encountered a number of difficulties. In the first place, precipitating sera, such as those used by us, are no longer active when diluted more than 1 to 20, or 1 to 40. This places a narrow limit upon the applicability of the method, as it may be necessary during the process of absorption to dilute the serum beyond its effective precipitin-concentration. When dilution of the serum is avoided, the so-called "prozone" may interfere with the formation of a precipitate during the phase of absorption. In many mixtures of undiluted serum and a concentrated solution of its protein antigen no precipitate occurs, yet when the mixture is diluted, the precipitate appears. In this case, of course, neither the antigen nor antibody is removable by centrifugation, and the delayed precipitation due to the first reaction often occurs when salt solution or the diluted antigens to be tested are added subsequently. It may be that the hydrogen-ion concentration of the fluids is a factor of prime importance in the precipitin reaction. A concentration of hydrogen-ions in the region of the isoelectric point of serum globulin may permit a precipitin reaction to progress to completion even in mixtures of undiluted immune serum and concentrated solutions of proteins. We have not investigated this point thoroughly. The results, however, of our experiments with the absorption of precipitins are unequivocal when the "ring-test" is used, readings of the precipitate at the junction of serum and antigen solutions being taken within one or two hours after the one has been layered upon the other. When allowed to stand for 18 hours or more, a slow precipitation often occurs in all sera, including the controls, showing that the original reaction had not been complete but was continuing under the conditions permitted by the subsequent dilution.

TABLE III

ABSORPTION OF PRECIPITINS

Anti-serum	Absorbed with	Precipitation with	Dilution of antigen					
			0	1-10	1-100	1-500	1-1000	1-2000
Anti-human serum 161.	Bence-Jones, No. 4.	Human serum.	++++	++	++	+	0	..
		Bence-Jones, No. 4.	0	0	0	0	0	..
		Simpson	+	+	+	0	..	..
		Farrel	+	+	+	0	..	..
	Bence-Jones, Simpson.	Human serum.	+++	++	++	+	0	..
		Bence-Jones, No. 4.	0	0	0	0	0	..
		Simpson	0	0	0	0	..	..
		Farrel	0	+	±	0	..	..
	Bence-Jones, Farrel.	Human serum.	++	++	+	+	0	..
		Bence-Jones, No. 4.	0	0	0	0	..	..
		Simpson	0	0	0	0	..	..
		Farrel	0	0	0	0	..	..
	0.85 per cent salt solution.	Human serum.	++++	+++	++	+	±	..
		Bence-Jones, No. 4.	0	0	0	0	..	..
		Simpson	+	+	+	0	..	..
		Farrel	+	+	+	0	..	..
Anti-Bence-Jones, Farrel, 195.	Human serum	Bence-Jones, Farrel.	++++	++++	+++	++	++	+
		Human serum.	0	0	0	0	..	..
	0.85 per cent salt solution.	Bence-Jones, Farrel.	++++	++++	++++	+++	++	++
		Human serum.	0	+	±	0	..	..

The technic used in absorbing the precipitins was as follows: With precautions to prevent bacterial growth in the tubes, 1 c. c. of antiserum was mixed with 1 c. c. of a 2 or 4 per cent solution of a Bence-Jones protein. This mixture was incubated at 37° C. for 24 hours, placed in the ice-chest for 18 hours and then centrifuged until clear. The usual series of tests and controls were then made with this absorbed serum, diluted one to two as a consequence of the addition to it of an equal quantity of the antigen for the phase of absorption. A control to determine the effect of simple dilution and manipulation upon the antiserum was made by carrying a mixture of equal parts of immune serum and salt solution through the stages of incubation and absorption.

Antihuman serum No. 161 was absorbed in this manner with 4 per cent solutions of the crystalline Bence-Jones protein, and the Farrel preparation of Bence-Jones protein, and with a 2 per cent solution of the Simpson Bence-Jones protein. To show the effect of the reversal of this procedure, an antiserum to the Farrel specimen of Bence-Jones protein was absorbed with human serum. The results of these absorption tests are summarized in Table III.

Several of the experiments summarized in Table III show again that antihuman serum does not precipitate the crystalline preparation of Bence-Jones protein (No. 4) and, further, that this Bence-Jones protein does not absorb precipitin from antihuman serum. The data demonstrate that by absorption of antihuman serum with certain preparations of Bence-Jones proteins it is possible to remove from this immune serum the precipitin responsible for the flocculation with solutions of these preparations, while only slightly lowering the titer of the serum for its homologous antigen, human serum. Confirmation of the result is obtained when an antiserum to one of these preparations of Bence-Jones protein (Farrel) is absorbed with human serum. The conclusion seems inevitable that some of these non-crystalline preparations of Bence-Jones proteins contain traces of human serum proteins, while, in this respect, the crystalline Bence-Jones protein acts as a single antigen.

COMPLEMENT-FIXATION REACTIONS

For the complement-fixation reactions antihuman serum was tested against the various Bence-Jones proteins, and antisera to the crystalline and Rosenbloom Bence-Jones proteins were tested against human serum. Preliminary titrations were made with all sera and solutions of the proteins to determine their anticomplementary action, and in the tests the anticomplementary controls contained twice the amount which did not inhibit hemolysis. This required the use of sera diluted one to two, and 1 to 20 dilutions of the solutions of Bence-Jones proteins. These dilutions, as has been pointed out, are just on the limit of effective concentration of precipitin. The results of the complement-fixation tests, therefore, indicate broad relationships, as closer interactions are lost through the dilution. In the tests, 0.25 c. c. was the unit volume of each component used. The usual antisheep amboceptor, with a titer of 1 to 3200, and guinea-pig serum as complement were employed. After the mixtures of antiserum, protein solution and complement were made, they were incubated in the water-bath at 37° C. for one hour. At the end of that time, three units of amboceptor were added, the 2.5 per cent suspension of sheep cells placed in the tubes, and all returned to the water-bath. Readings were taken at the end of one hour, or when all the proper controls had cleared. The results of these tests are collected in Table IV, in which ++++ indicates complete fixation (absence of hemolysis), and lesser degrees of fixation by proportionally fewer + signs.

The complement fixation reaction, according to this method, combines a differentiation based upon dilution of the antisera and antigens with the differences due to fixative power of

TABLE IV

COMPLEMENT FIXATION REACTIONS

Serum	Antigen	Conc.	Dilut.	Result
Anti-human serum, 161. Diluted 1–2.	Human serum.....	..	1–40	++++
	Bence–Jones protein:			
	No. 4.....	4%	1–20	0
	No. 1.....	4%	1–20	0
	Coag. R. urine.....	4%	1–20	0
	R. urine.....	..	1–20	+
	Taylor	4%	1–20	+
	Farrel	4%	1–20	+
	Simpson.....	2%	1–20	0
	Dine	4%	1–20	0
	X.....	4%	1–20	0
	Rosenbloom	4%	1–20	+++
Anti–Bence–Jones, No. 4. Serum 144. Diluted 1–2.	Bence–Jones, No. 4...	4%	1–20	++++
	Human serum.....	..	1–20	0
Anti–Bence–Jones, Rosenbloom. Serum 153. Diluted 1–2.	Bence–Jones, Rosenbloom.	4%	1–20	++++
	Human serum.....	..	1–20	0

specific precipitates. Its effect, therefore, is to indicate only broad relationships. The results thus obtained, as presented in Table IV, confirm the results of the precipitin reactions in showing immunological distinctions between Bence-Jones proteins and the proteins of human serum.

ANAPHYLACTIC REACTIONS

Anaphylactic reactions were studied upon the guinea-pig as a whole and on excised uterine horns of young virgin guinea-pigs. The animals in this series were actively sensitized, except where otherwise stated, by an intravenous injection of 0.25 c. c. of human serum or of a 4 per cent solution of a Bence-Jones protein. After an interval of approximately three weeks, the animals were tested by an intrajugular injection of serum or Bence-Jones protein. The data of these experiments are presented in Table V.

Anaphylactic reactions with the crystalline Bence-Jones protein were not as sharp as we desired, as it was difficult actively to sensitize guinea-pigs to this preparation. Both large and small doses of the crystalline protein were given on the first intravenous injection, and the animals were tested by a second intravenous injection of larger amounts after intervals of 18 to 27 days. With one series, fairly satisfactory results were obtained. The guinea-pigs of this lot received as the sensitizing dose injected intravenously 0.25 c. c. of a 4 per cent solution of the crystalline Bence-Jones protein (No. 4) on January 27, 1921. On February 14, 21 days later, an intravenous injection of 1 c. c. of the 4 per cent solution of No. 4 produced a severe but not fatal shock, in guinea-pig No. 396. None of 10 guinea-pigs thus sensitized to Bence-Jones protein No. 4 showed any reaction to human serum.

TABLE V

ANAPHYLACTIC REACTIONS

Guinea pig	Sensitizing dose	Interval	Intoxicating dose	Result
250	Human serum 0.25 c. c.	18 days	Human serum 0.25 c. c.	Typical anaphylaxis. Death, one min.
181	Human serum 0.25 c. c.	18 days	Bence-Jones No. 4. 2 c. c. 0.5% sol.	No reaction.
			10 minutes later: 2 c. c. human serum intraperit.	Typical shock. Death.
253	Human serum 0.25 c. c.	18 days	Bence-Jones No. 1. 7 c. c. 1% sol.	No reaction.
			10 minutes later: 1 c. c. human serum intraven.	Typical shock. Death.
251	Human serum 0.25 c. c.	18 days	Bence-Jones, Rosenbloom prep. 1 c. c. 4% sol.	Slight, definite reaction. Survived.
252	Human serum 0.25 c. c.	18 days	Bence-Jones, Taylor's prep. 1 c. c. 4% sol.	Slight, definite reaction. Survived.
173	Bence-Jones No. 1 2 c. c. 0.5% sol.	27 days	Human serum 0.25 c. c.	Typical shock. Death, one min.
275	Bence-Jones, Rosenbloom prep. 1.5 c. c. 1% sol.	18 days	Human serum 0.25 c. c.	Typical shock. Death, one min.
290	Bence-Jones, Taylor's prep. 1 c. c. 1.5% sol.	18 days	Human serum 0.25 c. c.	Typical shock. Death, two min.

The anaphylactic reactions summarized in Table V and in the above paragraph demonstrate a complete difference between the crystalline Bence-Jones protein and the proteins of human serum. On the other hand, guinea-pigs sensitized to human serum were also sensitive, though in less degree, to the Rosenbloom and Taylor preparations of Bence-Jones proteins, and guinea-pigs sensitized to these Bence-Jones proteins and to Bence-Jones protein No. 1 were extremely hypersensitive to human serum. From the results of the precipitin reactions, we are led to assume, in explanation of the crossed anaphylactic shocks, that the non-crystalline preparations of Bence-Jones proteins (No. 1, Taylor and Rosenbloom) contain traces of human serum proteins. These traces of serum proteins are sufficient to sensitize the animal to human serum, so that when a large amount of human serum is administered in the second injection, fatal anaphylactic shock occurs. Their content of serum proteins, however, is too small to produce a fatal reaction when they are injected in the amounts used by us into guinea-pigs primarily sensitized to human serum.

An analysis of these preparations of Bence-Jones proteins was permitted by the graphs obtained by the Schultz-Dale method.[15] The apparatus and solutions used in our studies of the anaphylactic reactions of isolated uterine muscle were essentially those described by Dale. Virgin guinea-pigs, sensitized to human serum or Bence-Jones proteins, were killed by a blow on the head about three weeks after the first injection. The uterus was removed, one horn was attached to the lever of a kymograph, and this strip of smooth muscle was then submerged in Ringer-Locke solution. The bath, 50 c. c. of Ringer-Locke solution, was kept at 37-38° C., and was supplied con-

FIG. 1.—Uterus of guinea-pig No. 1. Passively sensitized to Bence-Jones protein No. 4 by injection of 1 c. c. serum 144 into peritoneal cavity. Killed 18 hours later.
At A: 1 c. c. human serum.
At B: 1 c. c. 3% sol. Bence-Jones protein No. 4.
At C: 1 c. c. 3% sol. Bence-Jones protein No. 4.

tinuously with oxygen. Tracings of the movements of the strip of uterus were recorded on a smoked drum.

It was found more satisfactory passively to sensitize guinea-pigs to the crystalline Bence-Jones protein. This was easily accomplished by injecting intraperitoneally 1 c. c. of the serum of rabbit No. 144, which had been immunized to this Bence-Jones protein. The precipitin titer of this serum was 1 to 1,000,000, in terms of dilution of the antigen. Eighteen hours later, these guinea-pigs were found by tests to be hypersensitive to Bence-Jones protein No. 4.

Representative graphs, Figs. 1, 2 and 3, illustrate the results of some of the anaphylactic reactions with the isolated smooth muscle of the uterine horns of sensitized guinea-pigs. From Fig. 1 it is seen that the uterus of a guinea-pig sensitized to the crystalline Bence-Jones protein No. 4 did not react to human serum, and Fig. 2 shows that the uterus of a guinea-pig sensitized to human serum was not affected by the solution of this crystalline protein. Fig. 3 is of especial interest, as it is analogous to experiments on the absorption of antibodies. The uterus used in this test was from a guinea-pig actively sensitized to Rosenbloom's non-crystalline preparation of Bence-Jones protein. When treated with a solution of this Bence-Jones protein, a contraction occurred. A subsequent application of the same protein failed to cause a contraction, showing that the muscle was desensitized to that antigen. It, however, remained hypersensitive to human serum, as shown by the next phase of the curve, which records the contraction produced by the addition of human serum to the bath. After this second contraction, the uterus was specifically desensitized also to human serum. This analysis permits the definite conclusion that the Rosenbloom preparation of Bence-Jones protein is a mixture of a Bence-Jones protein and human serum proteins.

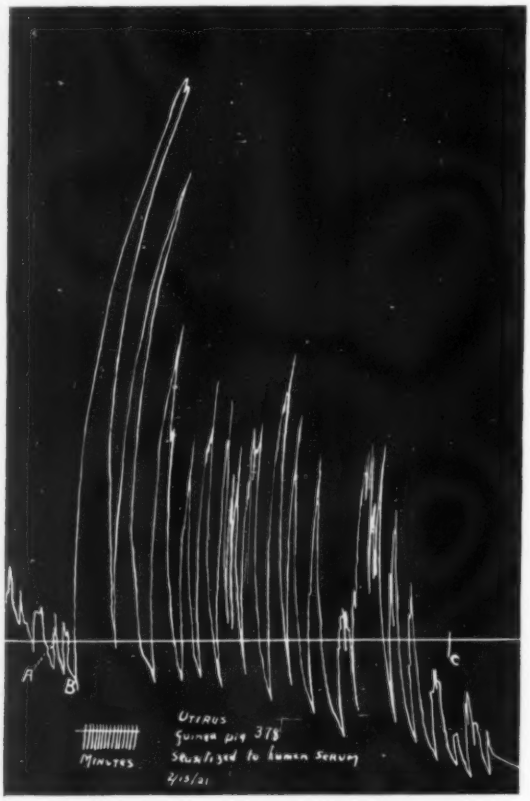


Fig. 2.—Uterus of guinea-pig No. 378, sensitized to human serum.
At A: 1 c. c. 4% sol. Bence-Jones protein No. 4.
At B: 1 c. c. human serum.
At C: 1 c. c. human serum.

Summary and Conclusions

In the possession of a crystalline Bence-Jones protein we had at our disposal an ideal substance for immunological studies. By crystallization, it could be freed from possible traces of serum proteins and thus permitted the use of a purified preparation to obviate the confused results which vitiate many immunological experiments. Its quality as an antigen was easily established, and the reactions dependent upon its antibodies were unequivocal. In contrast to this, the non-crystalline preparations of Bence-Jones proteins, precipitated from the urine by fractionation with salts or heat, gave the "cross" reactions usually obtained with mixed antigens. Comparisons between the Bence-Jones proteins and the proteins of normal human serum were made by the use of precipitin, complement-fixation and anaphylactic reactions. The precipitin reactions were extended by the method of the absorption of antibodies and the anaphylactic reactions were submitted to analysis by the Schultz-Dale method of the graphic record of the contrac-

Fig. 3.—Uterus of guinea-pig sensitized to Bence-Jones protein (Rosenbloom).
At A: 1 c. c. 4% sol. Bence-Jones protein (Rosenbloom).
At B: 1 c. c. same solution.
At C: 0.5 c. c. human serum.
At D: 0.5 c. c. human serum.

tion of smooth muscle. The results of all these experiments were in accord, and allow the following conclusions to be drawn:

1. The crystalline Bence-Jones protein acts as a single antigen.

2. The non-crystalline preparations of Bence-Jones proteins, isolated from the urine by salting-out or other precipitation methods, contain traces of serum proteins.

3. The Bence-Jones proteins are immunologically different from the proteins of normal human serum.

4. These differences between proteins from the same animal are further evidence in support of the conception that the specificity of proteins is not dependent upon their biological origin, but due to their chemical constitution.

BIBLIOGRAPHY

1. Bayne-Jones, S., and Wilson, D. W.: Proc. Soc. Exp. Biol. and Med., 1921, XVIII, 220-222.

2. Walters, W.: J. Am. Med. Assn., 1921, LXXVI, 641-645.

3. Wells, H. G., and Osborne, T. B.: J. Infect. Dis., 1913, XII, 341-358.

4. Woods, A. C.: Tr. Sect. Opth. Am. Med. Assn., 1917, 133-161.

5. Dakin, H. D., and Dale, H. H.: Biochem. J., 1919, XIII, 248-257.

6. Abderhalden, E., and Rostoski, O.: Ztschr. f. physiolog. Chem., 1905, XLVI, 125-135.

7. Rostoski: Münch. med. Wchnschr., 1902, XLIX, 740.

8. Boggs, T. R., and Guthrie, C. G.: Am. J. Med. Sci., 1912, CXLIV, 803-814.

9. Hopkins, F. G., and Savory, H.: J. Physiol., 1911, XLII, 189-250.

10. Cameron, A. L., and Wells, H. G.: Arch. Int. Med., 1915, XV, 746-753.

11. Massini, R.: Deutsch. Arch. f. klin. Med., 1911, CIV, 29-43.

12. Hektoen, L.: J. Am. Med. Assn., 1921, LXXVI, 929.

13. Friedberger, E., and Jarre, H.: Ztschr. f. Immunitätsforsch. u. exper. Therap., 1920, Orig., XXX, 351.

14. Krumwiede, C., and Cooper, G. M.: J. Immunol., 1920, V, 547-562.

15. Dale, H. H.: J. Pharmacol. and Exper. Ther., 1912, IV, 167-223.

YAWS

AN ANALYSIS OF 1046 CASES IN THE DOMINICAN REPUBLIC

By W. L. Moss,

Assistant Professor of Preventive Medicine and Hygiene, Harvard Medical School

AND

G. H. Bigelow,

Instructor in Preventive Medicine and Hygiene, Harvard Medical School

Historical Sketch of Santo Domingo

The island occupied by the Republics of Santo Domingo and Haiti is the second largest of the West Indian group lying between Cuba and Jamaica on the west and Porto Rico on the east. It lies between the 17th and 20th parallels of north latitude and between the 68th and 74th meridians.

Its 28,249 square miles of area are diversified by almost every variety of topography; fair and fertile valleys, broad savannahs, towering mountains, sinister desert. The northern half or two-thirds of the island is traversed by two almost unbroken mountain ranges, the Monte Christi and the Cibao or Cordillera, between which stretches from the sea on the west to Samana Bay on the east a beautiful valley, the "Vega Real," the eastern half of which is well watered and wonderfully fertile. It is in this valley and on the lower slopes of the adjacent mountains that most of the cacao and tobacco grow, which, with sugar, make up the chief exports of the island. Indeed the cacao crop of Santo Domingo is said to be the third largest of any country of the world. The southeastern part of the island is occupied by a broad coastal plain extending back from the Caribbean as much as 50 miles. This is occupied by broad savannahs, well watered and covered with a luxuriant growth of grass which would furnish excellent pasturage for vast herds of cattle. It is here that the great sugar estates are located which produce the largest single article of commerce of the island. Coffee is grown commercially to some extent in the mountains of the southwestern part of Santo Domingo toward the Haitian border.

Tropical fruits—bananas, plantains, pine-apples, cocoanuts, oranges, lemons, limes, mangoes, aguacartes, bread-fruit—flourish. Birds of brilliant plumage rival the gorgeous tropical flora in beauty. The fauna is curiously limited in some respects, the largest native mammal on the island being the agouti, a shy little beast somewhat resembling the guinea-pig in appearance and about the size of a rabbit.

The heat of the tropics is tempered along the coast by sea breezes, and by the altitude of the mountains in the interior, the highest peak, Loma Tina, rising 10,200 feet above sea level.

The commercial life of the island centers in the various ports scattered along the coast—Monte Christi, Puerto Plata, Samana, Sanchez, La Romana, Maccoris, Santo Domingo City and Barahona. The number of inhabitants in these towns varies from a few hundred in the smaller up to about 25,000 in Santo Domingo City, the capital.

The population of Santo Domingo, which occupies the eastern three-fourths of the island, is estimated at between 700,000 and 800,000 inhabitants, while Haiti, occupying the western fourth of the island, has a population of about two and a half million. Haiti is known as the Black Republic,

and takes pride in this appellation as indicating pure blood. The language is French. Santo Domingo, on the other hand, does not boast of its negro blood, although it is probable that considerably more than 75 per cent of the population possess it. In the larger towns, especially on the coast, there is a small white population, which shades down through all gradations of color to pure black. Few whites live in the interior, except in the occasional inland towns, the largest of which is Santiago de los Caballeros, a flourishing city of about 20,000 inhabitants, beautifully situated in the Vega Real. The language of Santo Domingo is Spanish.

Life in the interior is simple and furnishes little incentive for industry. The requirements for shelter and clothing are simply met and nature furnishes an adequate and healthful diet, with little exaction beyond the effort required to take it.

Perhaps few of us realize or remember the important part played by this obscure island in the history of Western civilization. Discovered on December 6, 1492, by Christopher Columbus, its present capital, Santo Domingo City, is the oldest existing European settlement in the Western Hemisphere. At the time Columbus landed and took possession of the island in the name of the King and Queen of Spain, calling it La Española, the native population consisted of Arawak Indians, estimated at between two and three million souls. Columbus described them as a mild and peaceful race, characterized by their sweetness of temper, the men of hideous visage but the women comely. They offered little resistance to the Spanish occupation, and their land was given by the King of Spain in huge grants to his favorites, who, attracted by the glowing descriptions of the wealth and beauty of the country, came over in large numbers, built palaces and cathedrals, set up a vice-regal court and lived in an extravagance which almost rivaled that of the court of Spain.

The Indians were easily subjugated, quickly reduced to a state of slavery, and under Spanish tyranny and cruelty were soon exterminated. The appalling rapidity with which this took place may be appreciated from the estimates of the population in the succeeding years. The two or three millions of Indians present in 1492 were reduced in a period of 15 years to 60,000 by 1507, and had been further reduced to 14,000 by 1514. Enrique, the surviving caique, was so enraged by the treachery of the Spaniards, which had led to the capture and execution of Queen Anacaona, that he fled with a small band of followers to the fastnesses of the mountains, where he successfully resisted all efforts to capture him. In 1533 the remaining Indians, 600 in number, under this chief were given lands and established at Boya, a small village within five miles of the camp at which the work we are to report was done.

With the Indians practically exterminated, the land with all its wealth of resources was of little value to its new possessors. To make it again profitable, the African slave trade was instituted as early as 1508. The cruelty and abuses practiced on the Indians were repeated on the Africans, and doubtless would have been attended by the same result, but for the fact that, as they were killed or died off, fresh importations were brought in. With the decline of the Spanish power the greatest blight to the existence of the slaves was removed, and under climatic and economic conditions, which were for the most part favorable, they multiplied so that the present population of Santo Domingo consists largely of descendants of the African slaves with a greater or less admixture of Spanish blood.

Although the history of the island abounds in interest we may not attempt even a brief sketch of it in this paper. In passing one may recall that it was from Santo Domingo that Cortez, Balboa, Pizarro and De Soto set out to make their brilliant explorations and discoveries. It was the rendezvous for many of the pirate craft that preyed on the British, Dutch and French commerce with the new world. Here the term "fillibuster" originated. The long speedy boats used in this piracy were called fly-bote or freibote, and their crews were known as freiboters, freebooters or fillibusters. The British and French united to retaliate against the Spanish pirates and established a base on St. Christopher and later on the island of Tortuga, just north of Santo Domingo, where they were joined by the Dutch. In addition to their operations on the water, they made frequent incursions into the northern part of Santo Domingo for the purpose of killing the cattle. Those who engaged in this pursuit came to be known as buccaneers, from boucan, the spit on which they cooked their meat.

From Tortuga the French gained a permanent foothold on the western end of the island, the part now occupied by Haiti.

Recall that the entire island has been at one time under Spanish rule, that the Dutch and British have each gained a foothold on the island, that eventually independence from France and Spain was gained, and the Republics of Haiti and Santo Domingo were established, that each of these young republics at one time or another gained possession of the entire island, and that these various changes were not effected without blood-shed. Indeed, the history of the island from the time of its discovery by Columbus in 1492 up to its military occupation by the United States in 1916 has been one of external war and internal revolution. Even in the short history of the republics, the list of presidents is of wearying length, the common way of removing a president being by assassination, and of establishing a new government, by revolution.

The result of this constant state of turmoil was that the resources of the island remained undeveloped, the people impoverished; a relatively large national debt was acquired, lawlessness prevailed, education and sanitation were sadly neglected.

Even in the few years during which the United States Military Government has been in control, splendid progress has been made in bettering these conditions. Peace has been maintained, law and order prevail, schools have been established, agriculture has been fostered, highways (one of the greatest essentials to the development of the country) constructed, and great progress has been made in sanitation. The credit for this work is due to the splendid group of U. S. Naval officers, who have been in charge of the military

government. The customs have been collected and not only have the expenses of this work been paid for, but the national debt which amounted to approximately $20,000,000.00 in 1907 has been reduced by about half.*

At the request of the military government of the Dominican Republic the School of Tropical Medicine, Harvard University, sent a commission consisting of Drs. A. W. Sellards, W. L. Moss and G. H. Bigelow to Santo Domingo during the summer of 1920 to study yaws. The results of the observations made are herewith presented in abstract.

CLINICAL DESCRIPTION OF YAWS

As the disease is strictly limited to tropical and subtropical countries, it may be unfamiliar to many physicians who have not been in the tropics; hence a brief introductory description of yaws is given.†

Synonyms.—Frambœsia tropica, yaws, buba, pian, etc.

Definition.—A tropical specific infectious and contagious disease caused by Treponema pertenue Castellani and characterized by a frambœsiform granulomatous eruption.

Distribution.—West Indies, Central America, northern part of South America, Africa, Malay Peninsula, Siam, Ceylon, parts of China. It is said never to occur in the mountains and cold districts and rarely above an elevation of 800 feet.

Etiology.—The Treponema pertenue, first observed by Castellani in 1905, is now accepted as the etiological agent of the disease. There has been much discussion concerning the question of the identity of yaws and syphilis, and while some observers still maintain their unity, the evidence at hand seems sufficient to establish them as two separate diseases. Charlouis, as early as 1882, successfully inoculated yaws in a syphilitic patient, and syphilis in a patient infected with yaws. That yaws patients are not immune against syphilis is further indicated by the observations of Powell and Nichols and of others, who have described cases of syphilis supervening on yaws.

Incubation Period.—Castellani gives the incubation period as from two to four weeks. Paulet, in 1848, inoculated 14 negroes with the secretions from frambœsic granulomata, and all developed yaws in from 10 to 20 days. In monkeys and other animals, experimentally inoculated with yaws, the incubation period varied from 16 to 92 days.

Symptomatology.—The course of the disease, like that of syphilis, may be divided into a primary, secondary, and tertiary stage. Some authors add a fourth stage (paraframbœsial affections), but it is questionable whether the observations on which this additional stage is postulated are reliable.

Primary Stage.—Incubation period two to four weeks, characterized by malaise, rheumatic pains, headache, sometimes irregular fever. The primary lesion (mother yaw, madre buba) appears as a papule, which after a week becomes moist, and develops a yellow secretion. A crust may form, which on removal reveals an ulcer with a granulomatous base. The primary lesion may heal before, but usually persists until after the secondary eruption has appeared.

Secondary Stage.—The secondary stage begins in from one to three months after the primary lesion, and is characterized by a general eruption of granulomata over the body. It is preceded by malaise, headache, severe pains in the muscles, joints and bones. In some cases there may be fever of an intermittent type. The granulomata appear first as minute papules, which increase in size to an average diameter of about one centimeter. They may coalesce, become secondarily infected, and form large ulcerating areas. In the majority of cases—within three to six months in children, and six to twelve months in adults—the granulomata dry up, shrink, and disappear. In some cases the granulomatous eruption may continue for several years, new crops of nodules appearing from time to time in succession. The granulomata generally undergo involution within from two to four months, leaving behind, as a rule, some change in pigmentation. At times secondary ulceration occurs, leading to deeper scars, and occasionally the granulomata take the form of a circinate eruption.

The granulomata frequently occur on the soles of the feet, less often on the palms of the hands, with a resulting condition closely resembling the syphilitic psoriasis palmaris and plantaris.

The alimentary, respiratory, excretory, and central nervous systems are rarely involved. The joints are frequently swollen and painful. Lesions of the mucosæ are rare. Castellani and Chalmers have not observed alopecia, but state that various groups of lymphatic glands are found enlarged. There may be a moderate degree of anæmia of secondary type and an increase in the large mononuclears. The Wassermann reaction is positive in the great majority of recent cases, but is fairly often negative in old cases.

Tertiary Stage.—The disease often terminates with the secondary stage. Sometimes the secondary and tertiary stages merge, or there may be an interval of years between them.

The characteristic lesions of the tertiary stage are gummatous-like nodules and deep ulcerative processes, frequently resulting in great deformity. The bones are quite commonly implicated, but visceral lesions are rare or absent. Castellani and Chalmers think that Gangosa, an ulcerative condition of the palate, nose, and pharynx, is in reality a tertiary manifestation of yaws.

Histopathology.—In the frambœsic papules the surface epithelium is greatly thickened and numerous elongated downgrowths are seen. In patches the epithelial cells are swollen, vacuolated and degenerating. Circumscribed areas contain polymorphonuclear leucocytes. The layers near the corium are almost normal, but the corium itself is œdematous. There

* For the history of Santo Domingo the reader is referred to two fascinating books: "Santo Domingo—A Country with a Future," by Otto Schoenrich; and "Santo Domingo, Past and Present," by Hazzard; both unfortunately out of print. Free use has been made of these and of the Encyclopedia Britannica in the brief historical note here given.

† This description is taken largely from the chapter on Frambœsia Tropica, Manual of Tropical Diseases, Castellani and Chalmers, Third Edition, Wm. Wood & Co., 1920.

is a diffuse cellular infiltration consisting of polymorphonuclear leucocytes, large and small mononuclears, eosinophiles, plasma cells, mast cells, connective-tissue cells and some extravasated erythrocytes. Treponemata are present in the granulomata.

Treatment.—Brodin in 1910 tried antimony. "Castellani's Yaws Mixture" contains tartar emetic, potassium iodide, sodium salicylate, and sodium bicarbonate. Salvarsan was first used by Nichols in the experimental disease in monkeys, and by Strong in the treatment of the disease in man. The cure of yaws with salvarsan or neo-salvarsan is one of the most striking examples of specific therapy that medicine presents.

The malady does not appear to be hereditary. The course of the disease is chronic, resulting in serious disability and much suffering in a majority of cases. The mortality from yaws is not high, and death, when it occurs, is usually due to secondary infections.

The Authors' Observations

In discussing the cases observed by us in Santo Domingo the following abbreviations are used for convenience of reference. If the reader will take a moment to familiarize himself with these, the understanding of what follows will be facilitated:

M. Madre buba, mother yaw, primary lesion.

B'. Florid secondary eruption of granulomata. Early secondary stage.

B. Sparse recurring secondary granulomata. Late secondary stage.

C. Clavus. Late lesions on the soles. Late secondary stage.

P. Palmar lesions. Late lesions on the palms. Late secondary stage.

G. "Gomma." Tertiary stage.

H. History of yaws. No active lesions present. Quiescent.

PRIMARY STAGE

We observed 64 cases in which a primary lesion was present, sometimes alone, oftener in combination with other manifestations of the disease. Briefly these cases may be presented in the following tabular form:

Diagnosis	No. of cases	Average age in yrs.	Average duration in mos.
M	15	6.6	2.3
MB'	25	8.5	7.3
MB'C	13	11.6	4.1
MB	6	24.2	19.0
MBC	5	10.	17.2

The extremes of age in this group of cases were 7 months and 60 years. The duration of the madre at the time of observation varied from one month to six years, and the size varied from 1 to 7 cm. with an average diameter of about 2.5 cm. Of the 15 cases in the above group which presented a madre buba as the only active lesion, five showed healed scars of secondary granulomata; thus there were only 10 cases which had not progressed beyond the primary stage. In 54 cases, or 84 per cent, of our series, the madre persisted after the appearance of secondary lesions.

Location of Primary Lesion.—In 969 cases the location of the madre was determined either by history, observation of the lesion, or scar (in 635 cases, or 71 per cent, the scar was present). In 18 additional cases the patients stated that they had had no madre but that multiple granulomata had appeared simultaneously over the body. In two cases the patients claimed to have had two madres simultaneously.

Table Showing Location of Madre

	Cases	Approx. per cent
Lower extremities	803	82.87
Upper extremities	80	8.26
Head	39	4.02
Trunk	37	3.82
Genitalia	10	1.03
	969	100

The primary lesion occurred on the right side of the body in 425 cases and on the left side in 468 cases. In the remaining cases, the site was noted as knee, ankle, etc., but the side of the body was not recorded.

These figures have been analyzed to determine if the site of the madre might throw any light on the mode of transmission of the disease. In this connection it is to be remembered that we are dealing with a bare-footed and bare-legged population, that even the adults are scantily clothed, that the upper extremities are almost as much exposed as the lower, and that children of both sexes usually wear no clothing until they are about five years of age.

Sexual Transmission.—Sexual transmission as a common method may be excluded because of the fact that in only 1 per cent of our series was the primary lesion on the genitalia. Of these 10 individuals, 6 were males, 4 females, and 5 were under 8 years of age. Moreover, in 25 per cent of all the cases in our series the infection occurred before the fifth year of life.

Hereditary Transmission.—We saw no evidence of hereditary transmission in any case.

Insect Transmission.—We think that transmission by the bites of the common flying insects, such as flies, mosquitoes, etc., may be excluded on the basis of the distribution of the primary lesion; in the great majority of cases, the madre occurred on the lower extremities, whereas the face and upper extremities are equally exposed to the bites of these insects.

The preponderance of the primary lesion on the lower extremities as compared with the trunk would likewise seem to exclude transmission by the bites of such non-flying insects as lice, fleas, bed-bugs, and the like.

The fact that in such a large majority of cases (83 per cent) the primary lesion occurred on the lower extremities led to a further analysis of these cases. The result is shown in the

following tabulation, and for comparison the figures for the upper extremities are given:

	Cases		Cases
Buttocks	13	Shoulders	6
Thighs	30	Upper arms	4
Knees	55	Elbows	16
Legs	201	Forearms	17
Ankles	258	Wrists	8
Feet	246	Hands	25
Total	803	Total	76

It will be noticed that the frequency with which the primary lesion is found on the various parts of the lower extremities increases strikingly as one approaches the ground. This suggests that if the disease is transmitted by the bites of insects, we should think of some non-flying insect which remains on or near the ground, and does not normally prey on man or even desire to domicile with him; such as ants, ground spiders, and the like.

The possibility that trauma provided the portal of entry for the treponema has been suggested. The greater frequency of the primary lesion on the exposed parts of the body fits in with such an hypothesis. It seems probable also that in a bare-footed population the lower extremities would be the most frequently traumatized part of the body, and that the frequency of minor injuries would increase as one progressed down the extremity. Examination of the preceding table shows that the frequency with which the madre occurs on the various parts of the lower extremities increases as one descends toward the foot.

Man, being a forward-going animal, is apt to get most of his knocks from in front; accordingly, we have analyzed the primary lesions occurring on the knees, legs and ankles with reference to their occurrence on the anterior, external, internal and posterior surfaces.

As far as our records showed this data, the results are set forth in the following table:

	Anterior	External	Internal	Posterior
Knees	18	8	6	4
Legs	107	35	19	12
Ankles	25	79	84	13

In the case of the knees and legs it is shown that the anterior surface leads by a large majority, the external surface comes next, followed by the internal surface, while the posterior surface finishes a poor last. This probably corresponds closely to the exposure to minor traumata.

In regard to the ankle the circumstances are different. Owing to its conformation the malleoli are about equally exposed to injury, while the anterior surface of the ankle is protected by the projecting foot which receives on its dorsum the injuries which would otherwise go to the ankle. This corresponds with the frequency of the madre on the various parts of the ankle, and with the fact that in the case of the foot, the primary lesion was found on the dorsum in a great majority of cases.

It appears probable from our observation, therefore, that trauma, frequently minor in character, usually determines the site of the primary lesion in yaws. This is entirely compatible with the view that the disease may be transmitted by direct contact, or that insects, flies, etc., may be vectors of the virus.

SECONDARY STAGE

Florid Secondary Stage.—In our series there were 144 patients who presented themselves during the florid secondary stage of the disease. In 38 of these the primary lesion was still present and in 37 the late lesions of the soles, known as clavus, had made their appearance.

Briefly summarized these cases are presented in the following table:

FLORID SECONDARY STAGE

Diagnosis	No. of cases	Avg. age	Avg. duration	No. of cases with fresh granulomata on soles	No. of cases with fresh granulomata on palms
MB′	25	8.5 yrs.	7.3 mos.	2	1
MB′C	13	11.6 "	4.1 "	7	1
B′	82	8.8 "	12.3 "	6	0
B′C	24	12.9 "	30.4 "	9	2
	144			24 (16.6%)	4 (2.8%)

Exclusive of the 38 still showing the primary lesion and previously analyzed, the youngest patient in this group was 1 year and the oldest 50 years.

While clavus may develop very early in the disease, witness the 13 MB′C cases with an average duration of 4.1 months, as a rule it does not develop until the disease has lasted more than a year. The average duration in the 82 patients who presented only secondary granulomata was 12.3 months, whereas the average duration of the cases which showed clavus in addition to the florid secondary eruption was 30.4 months. The greater frequency of granulomata on the soles as compared with the palms is indicated by their presence in the former situation in 16.6 per cent of this group as against 2.8 per cent in the latter situation.

From our observation and the histories we obtained, we are led to believe that, in the disease as it occurs in Santo Domingo, practically all of the patients, sooner or later, develop granulomata on the soles and become the victims of the painful condition which they designate as clavus.

The secondary eruption, as we saw it, corresponds closely to the text-book description as given by Castellani and Chalmers. The individual granuloma does not differ materially in appearance from the primary lesion except that it usually does not become so large and seems less apt to undergo as deep ulceration. In our notes we described the earliest stage observed by us, as a small papule 1 to 2 mm. in diameter, gray in color, and surrounded by a narrow zone of hyperemia. These papules increase rapidly in size to an average diameter of about 1 cm. and are usually elevated 0.5 to 0.75 cm. above the skin. The surface of the granuloma is covered with minute

bosses which give it a raspberry-like appearance from which the disease takes the name *frambæsia* (Figs. 4, 5, 6, and 8). In the early stage the granulomata are of a pearly gray color; later they are apt to become covered by a thin yellow crust. After a few weeks or months retrogressive changes take place; the lesions turn dark, often black in color, shrink in size, the surface becomes checkered, and after a time all that remains is a black crust, which on falling may leave no scar; more frequently pigmentary changes persist, which may consist of increased pigmentation, apigmentation or an apigmented area surrounded by a zone of increased pigmentation.

At no stage of the granulomata was vesiculation noted. They may go through their entire existence without ulceration, but more frequently they become secondarily infected, and consequently more or less deeply ulcerated. During the florid secondary eruption there may be hundreds of granulomata over the body, and no part of the cutaneous surface, from the crown of the head to the soles of the feet, is exempt from invasion. They show a special predilection for the muco-cutaneous borders—nostrils, mouth, genitalia, anus, and moist surfaces—axillæ, internatal region, between the upper thighs and popliteal spaces (Figs. 7 and 8). The mucous membranes are said to be rarely involved and we saw but one such case in our series, a single granuloma on the vermilion surface of the lower lip. We observed no case of alopecia except as the result of ulcerative processes involving the scalp. One patient presented the typical circinate arrangement of the lesions on the face, which strikingly suggested the Indian war-paint appearance (Fig. 12).

Usually there was no complaint of pain in consequence of granulomata on the body except in cases in which they were situated on the bearing surfaces of the feet, on the palms of the hands or when extensively ulcerated.

Arthritis (Fig. 22) and dactylitis were fairly common, although they usually occurred later than the florid secondary stage of the disease. The knee-joints were involved most commonly, the elbows next in frequency. Usually a single joint was affected. The swelling was sometimes considerable and in one instance as much as 200 c. c. of slightly turbid, straw-colored fluid was aspirated from a knee-joint. This fluid was without evident effect when injected into the peritoneal cavity of a guinea-pig. The dactylitis took the form of the usual spindle-shaped fingers, generally a single digit, sometimes several, being involved.

Late Secondary Stage.—There were 190 cases in the series that were considered to be in the late secondary stage of the disease. The patients had passed through the florid secondary eruption as evidenced by the numerous scars of previous granulomata. Many of them had doubtless been entirely free from active lesions for variable lengths of time after which one or more recurrent granulomata had appeared. It is evident from the histories obtained that the disease may undergo an apparent spontaneous cure, but sooner or later granulomata reappear in a majority of cases and successive crops, consisting usually of only a few lesions, continue to make their appearance, with free intervals between for many years. Briefly tabulated these cases may be presented as follows:

LATE SECONDARY STAGE

Diagnosis	No. of case	Avg. age	Avg. duration	No. of cases with fresh granulomata on soles	No. of cases with fresh granulomata on palms
MB	6	24.2 yrs.	19 mos.	2	1
MBC ...	5	10.0 "	17.2 "	1	1
B	60	9.3 "	29.6 "	16	1
BC	106	16.5 "	5.4 yrs.	69	1
BCP ...	13	20.5 "	11.3 "	10	4
Total..	190			98 (51.6%)	8 (4.2%)

Of the 190 patients in this group, 60 had as their only active manifestation of the disease a few secondary granulomata, 106 had granulomata plus clavus lesions and 13 had, in addition to the above, palmar lesions. Eleven cases which have already been analyzed with the madre cases are included here, as they appear to have been in a late secondary stage of the disease in spite of the persistence of the primary lesions.

The extremes of age in this group are 1 and 75 years; and while the former figure shows that a late secondary stage may be reached not only early in life but comparatively early in the disease, the average age in this group indicates that this is exceptional, and both the average age and average duration of the disease at the time of observation point to the chronicity of the secondary stage of the disease.

CLAVUS.—Perhaps the most curious and interesting effects of the disease are the late lesions which occur on the soles of the feet and it is to these that much of the pain and disability is due. We have adopted the term "Clavus" used by the natives, because it seems an appropriate one, although they use it to designate conditions of the soles long after anything suggesting a "Nail" has disappeared.

In a previous section attention has been called to the frequency with which secondary granulomata appear on the soles. Those occurring in this situation do not differ materially in appearance from granulomata seen elsewhere on the body (Fig. 13). They are perhaps more frequently secondarily infected, and are apt to ulcerate, probably as a result of the fact that the natives seldom protect them by any sort of dressing and continue to hobble about even when the feet appear to be in a shocking condition.

If the granuloma on the sole heals without ulceration, as it shrinks, it separates from the surrounding epidermis and becomes circumvallate. The hard, dry black core must act like a foreign body beneath the foot and it is the "nail" which led to the use of the term clavus. Finally, the core drops out leaving the "nail hole," a circular opening 0.75 to 1 cm. in diameter with sharp-cut edges which descend vertically 2 or 3 cm. to a flat base.

Usually both soles are about equally involved, although rarely cases are encountered in which only one sole is affected (Fig. 15). The number of granulomata on each sole may vary from only a few to 20 or 30. Irregular erosion, the result of attrition of the epidermis intervening between the "nail holes" may account for the remarkable moth-eaten appearance

of the soles which many of the old clavus cases present (Figs. 14, 17 and 18).

Under the designation "clavus" the natives include conditions differing from those just described and which are not so readily explained as the result of pre-existing granulomata. Not infrequently the soles presented a condition which is aptly described by the term honey-combed. The entire sole, or, in some cases only the bearing surface, was filled with pits 0.5 cm. or less in diameter, conical in shape and extending to a depth of 2 or 3 mm. These pits are as closely and regularly set as the cells of a honey-comb, and no such number or distribution of fresh granulomata was observed as would suggest that each pit could represent the site of a previous tumor.

In other cases the epidermis of the entire sole or a large part of it was greatly thickened, black, and dead-looking.

The natives applied the term clavus indiscriminately to any of the conditions just described. Pain was the characteristic common to all. Like the granulomata elsewhere on the body, the clavus lesions would clear up spontaneously in time, only to recur again and again throughout many years.

Occasionally a condition of the soles was seen to which the natives apply the name "Rajadura," which means a fissure or crack. The fissures, 2 to 3 cm. long and 2 to 3 mm. deep, are usually arranged vertically about the periphery of the heel. More rarely they occurred in the sole beneath the instep or ball of the foot, where they might attain a length of 6 or 8 cm., reaching to a considerable depth and, like those of the heel, cause much pain. We gained the impression that these fissures were also due to yaws, and for this reason have included in our analysis the relatively small number of cases encountered with clavus, although the term "Rajadura" is more descriptive.

Before proceeding to the analysis of the clavus cases it may be well to state that we have not included in this category any cases which presented fresh granulomata as the only lesions of the soles. We have reserved the term clavus to designate only the late effects of the infection on the soles, and think that these should be regarded as belonging to the late secondary stage of the disease. It may be of interest to give here a description of the changes which took place in the clavus cases following the administration of neo-salvarsan leading to their cure. A statistical statement of the result of the treatment in all cases will be given in a later section of this paper, but the results obtained by treatment furnished corroborative evidence that these several different lesions were properly considered as a manifestation of yaws.

We were prepared to expect the improvement which resulted from the use of neo-salvarsan in the cases with fresh granulomata, whether they were situated on the soles or elsewhere on the body, but it seemed rather too much to expect that these old "moth-eaten," dilapidated soles would be rejuvenated by a few injections of any drug. The first few patients were given an injection more as a placebo on account of their importunity and the long distances that some of them had come, rather than with any expectation that they would be benefited. When these patients came back at the end of a week, however, their feet not showing the least improvement in appearance, we received with surprise and incredulity the statement that they were cured of pain and when they adduced, in support of their claim, the statement that, whereas they had been obliged to come on horse the first time, they were able to return on foot, we were encouraged to try treatment on other cases. In the end clavus comprised the largest and in certain respects the most important group of cases that were presented for treatment.

A week after the first injection of neo-salvarsan there was, as a rule, no objective change in the feet, but almost without exception the patients affirmed that the pain was either greatly ameliorated or entirely gone. The injections were usually given at from seven to ten day intervals. About a week after the second injection, the old dead epidermis loosens up about the edges of the clavus holes, erosions and fissures, and begins to desquamate. This process goes forward rapidly until within a week or two after the second injection all the old epidermis has been shed, exposing healthy pink skin.

The following table summarizes the clavus cases:

Diagnosis	No. of Cases	Avg. Age	Avg. duration	Sole affected: Right	Left	Both
MB'C	13	11.6 yrs.	4.1 mos.	8	11	6
MBC	5	10. "	17.2 "	4	4	3
B'C	24	12.9 "	30.4 "	21	23	20
BC	106	16.5 "	5.4 yrs.	94	92	80
BCP	13	20.5 "	11.3 "	11	13	11
C	327	21.6 "	9. "	299	291	266
C+*	41	29.4 "	12.9 "	33	35	27
CP	50	32.7 "	18.7 "	45	47	42
	579			515	516	455

In 3 of the 579 clavus cases no note was made as to which sole was involved. It is apparent, however, that the right and the left sole are affected with equal frequency, and that in a majority of cases both soles are implicated (79 per cent in the above series).

Although we have seen clavus in an infant of one year, attention is called to the fact that the average age of the largest group in this series, the 327 patients who had clavus only, was 21.6 years, and that the average duration † of the disease in this group at the time they presented themselves for treatment was 9 years.

Palmar Lesions.—Perhaps corresponding to the clavus lesions, though not so definitely dependent upon granulomata, are the painful keratoses and fissures which, late in the disease, appear on the palms of the hands. There is sometimes more or less erosion of the epidermis and frequently an inability to open the hand fully and extend the fingers. This is apparently due to a certain amount of contraction of the hard, dry keratosed surface.

* The group of 41 cases designated as C+ had in addition to clavus some other condition which apparently was not dependent on the yaws infection. In a majority of cases the additional affection consisted of chronic leg ulcers.

† Wherever average duration is given in this paper it refers to the duration since the first appearance of the primary lesion and not to the duration of any particular stage, unless so specified.

The condition is usually painful, though less so than clavus, and interferes with manual labor. It is a much rarer lesion than clavus, and appears to develop in older individuals and later in the disease, though it seems to be equally amenable to treatment.

In our series this condition was met with 68 times, but only five of these patients had palmar lesions (exclusive of scars) as the only effect present. These 68 cases are briefly summarized in the accompanying table:

Diagnosis	No. of cases	Average age	Average duration
BCP	13	20.5 yrs.	11.3 yrs.
CP	50	32.7 "	18.7 "
B	5	25. "	14. "

It is rather striking that of the cases presenting a single manifestation of yaws, clavus forms the largest group, 327 cases, while those showing palmar lesions (other than fresh granulomata) constitute the smallest group—five cases. It is also striking in the above summary of the palmar cases, that those associated with clavus as the only other lesion form the largest number—50 out of 68 cases.

It is interesting that the average duration of the disease in the *CP* group, 18.7 years, is the longest of any group of the entire series, not excepting those in the tertiary stage of the disease.

Studded Lesions.—In a number of cases we observed nodular skin lesions which we believe to be a manifestation of yaws (Fig. 20). The earliest stage of these nodules was either not observed or else was not recognized as the beginning of lesions which in a later stage of their development became quite familiar to us. Apparently, these lesions may occur on any part of the body, although we never observed them on the head or face. The forearms and legs were the commonest sites in the cases which we observed. The thighs and trunk were frequently implicated and lesions starting on the dorsum of the foot and extending on to the plantar surface were noted.

A typical picture of the condition as observed by us may be described as follows: The individual lesion consists of a moderately hard skin nodule, 1 cm. in diameter, elevated 3 to 4 mm., not painful, unaccompanied by itching and without striking pigmentary changes until after regression, when increase of pigment may mark its former site. These nodules are thickly studded and regularly set over an area 8 to 10 cm. in diameter. The size of the area involved increases by an advancing margin consisting of an almost unbroken row of nodules. As this peripheral advance occurs, healing takes place in the center of the area. If the nodules do not ulcerate this retrogression is accompanied by desquamation of the epithelium. The nodules gradually flatten out and finally disappear, leaving no trace, or more often a circular area of increased pigmentation.

In no case were the nodules observed to pass through a vesicular stage, but they frequently underwent ulcerative changes varying from very superficial ulceration involving only the individual nodules to extensive and deep ulceration which sometimes became confluent over large areas of the body and extended to the subcutaneous tissues. The degree and character of the resultant scarring probably depends upon the depth to which the ulceration had extended. Sometimes there remains only an increase of pigmentation, as mentioned above; sometimes the skin over the entire area involved was left thin and crinkly and in patterns like those which form on the surface of hot chocolate which has been thoroughly boiled and allowed to stand awhile. Again, where the ulceration has extended to a greater depth there may result complete leucoderma and sometimes painful keloid (Fig. 21).

We have called these lesions "studded" for the lack of a more descriptive term. The area involved, when small, is usually circular, but as it increases in size it is apt to become elliptical or more often it approaches a rectangular shape but with rounded corners. If situated on an extremity, the long diameter of the area coincides with the axis of the limb. Seldom does it completely encircle an extremity even when large areas are involved.

We regret that we had no opportunity of studying these lesions histologically. They do not in the least resemble the primary and secondary granulomata. We do not know if they should be considered a late secondary manifestation of the disease or if they belong to the tertiary stage.

We have notes on 37 cases, the youngest patient exhibiting these lesions being 5 years of age and the oldest 80 years. The average age in this group was 28.8 years, which comes next in length to the gomma group (29.3 years). The average duration of the disease (yaws) in this group was 13.5 years with the extremes of duration 5 months and 39 years. This average duration is exceeded only by the P, G, and CP groups.

Our belief that these skin lesions are a manifestation of yaws is based on the fact that they were observed only in patients who gave a history of yaws, or who had other recognized yaws lesions, and on the observation that they apparently responded specifically to neo-salvarsan therapy.

We are inclined to regard them as a late secondary manifestation of the disease.

Tertiary Stage

The impression gained from a fairly close study of over a thousand cases leaves no doubt in our minds that yaws and syphilis are separate diseases. Exclusive of the evidence contained in the literature of inoculation experiments, the occurrence of yaws and syphilis in the same patient, the difference in the response of the two diseases to mercury, the possibility of reinoculation in yaws, the localization of the disease to the tropics and below certain altitudes, the grounds afforded by our own experience on which we base our opinion are as follows: Syphilis is universally recognized as a venereal disease, the primary lesion is, in the vast majority of cases, located on the genitalia and even in the cases not contracted through sexual intercourse, in which the primary lesion is extra-genital, the course of the disease is in no way modified by the method of inoculation or the unusual seat of the chancre. Yaws, as we have already pointed out, can be excluded from the category of venereal diseases by the fact that in a series of approximately

a thousand cases the primary lesion was located on the genitalia in only 1 per cent and infection took place in 25 per cent before the fifth year of life. Moreover, the primary lesion in yaws differs distinctly in appearance from chancre, even when the latter is extragenitally located, the madre buba, as a rule, being larger, the surface rougher; moreover, in no case was there the hardness sometimes present and usually considered characteristic of the syphilitic lesion.

In no case did we observe any evidence or obtain any history of hereditary transmission of the disease.

The duration of the madre buba and the high percentage of cases in which it persists after the onset of the secondary stage of the disease (84 per cent in our group of 64 madre cases) is contrary to what is observed in syphilis.

When we come to consider the secondary stages of the two diseases we find more striking contrasts and more especially do we note the remarkable pleomorphism of the secondary lesions of syphilis and the faithful monotony of the secondary granulomata of yaws. The versatile *Spirocheta pallida* may occasionally produce a counterfeit yaws but never did we observe a yaws patient in the secondary stage of the disease who failed to show either typical granulomata or scars which we felt sure were the marks of typical granulomata. Even the secondary infections and ulcerations which may result do not disguise the nature of the lesions.

Although Castellani and Chalmers say that "occasionally, peeling, whitish patches may be seen on the palms of the hands and soles of the feet closely resembling the syphilitic psoriasis palmaris and plantaris" we have never observed in syphilis anything resembling the clavus and palmar lesions which we have described as occurring in yaws. On the other hand, none of the yaws cases which we observed presented such characteristic secondary manifestations of syphilis as the macular skin rash, mucous patches and alopecia.

In the tertiary stage of the disease the absence of visceral involvement especially of the heart, blood vessels, liver and kidneys is in striking contrast with the frequency of their involvement in syphilis. Moreover, in a series of over a thousand cases in which the average duration for the entire series was 20.3 years and 79 of which were in the tertiary stage, none showed any evidence of central nervous system involvement. We do not wish to attach undue significance to the absence of central nervous system lesions in this series of cases because the relative immunity of the colored race to such involvement in syphilis is well known.

Finally, the marked difference in the response of yaws and syphilis to neo-salvarsan is a not unimportant point in favor of the duality of the two diseases. We have seen the lesions of a patient in the florid secondary stage of the disease melt away completely after a single injection of 0.6 gm. of neo-salvarsan. Indeed the cure of yaws by this agent is the most dramatic therapeutic performance that we have ever witnessed.

But although a decision between syphilis and yaws in the primary and secondary stages was arrived at with little difficulty, there were cases presenting tertiary lesion in which we found it impossible to make the differential diagnosis (Figs. 23, 24, and 29). There were patients with periosteal thickenings of the long bones; especially of the tibia, radius and ulna. There were those with typical spindle-shaped swellings of one or more fingers, and others with the bridge of the nose destroyed and with perforation of the hard and soft palate (the condition known as gangosa). There were cases in which old ulcerative processes had led to loss of substance of the cranial and other bones. Some of the patients who had an eye that had ulcerated out, and some in whom the nose was almost completely destroyed or fingers or toes had been lost, suggested the ravage of leprosy. Whether these results were due to syphilis or yaws we are unable to state positively. The patients themselves applied the term "Gomma" to all tertiary lesions and stoutly maintained that they were due to the latter disease "yaws."

There were other patients exhibiting tertiary manifestations which bore no resemblance to syphilis as we see it in the United States to-day. These included extensive skin ulcerations, great enlargement and deformity of the hands and especially of the legs and feet.

As previously mentioned, pain in the joints and often an effusion was a frequent complaint in the secondary stage. Many of the tertiary cases showed arthritic enlargement and partial or complete fixation.

That those cases objectively indistinguishable from syphilis, were actually yaws, we must, of course, leave unsettled. In favor of the view that they were yaws are the following facts:

The patients themselves, who are familiar with both diseases, maintained that the condition from which they were suffering was yaws. Practically all of this group denied having had syphilis (this denial deserves some consideration, because little or no shame attaches to venereal infection among the natives). There were 79 individuals in the "Gomma" group and of these 67 were able to give the location of the primary lesions. Corroborative evidence of the correctness of their statements as to the location of the primary lesion was furnished by a scar in 34 cases. In only two of the 67 cases was the location of the primary sore at all a usual one for a chancre, the upper lip in one case and perineum in the other.

SUMMARY OF THE GOMMA CASES

Diagnosis	No. of cases	Average age in years	Extremes	Duration in years Average	Duration in years Extremes
G	67	29.3	3-85	16.3	7/12-59
MG	1	25.2	7-60	9.7	1-40
BG	3				
BCG	2				
CG	5				
CPG	1				

The youngest patient in the entire gomma group was 3 years, the oldest 85 years. The average age for the entire group, as well as the duration of the disease at the time of observation, was greater, as would be expected, than in any other group with the exception of the cases with palmar lesions. The extremes both of age and duration are strikingly far apart.

It is of interest that in one case the primary lesion persisted after tertiary manifestations had made their appearance.

That the disease may progress to the tertiary stage in a comparatively short time is shown by the fact that in 10, or 7.9 per cent, of the gomma cases the disease had existed 2 years or less at the time of observation.

Latent Yaws

We have included in our series 127 individuals who had no active lesions of yaws at the time they were observed but who gave a history of having had the disease and who, in most cases, exhibited confirmatory evidence in the way of scars. Brief histories were taken and examinations made of all these cases, inasmuch as they furnished certain statistical data of some interest. Moreover, being impressed with the chronicity of the disease, the frequent recurrence of active lesions after longer or shorter periods of latency, with the doubt in our minds that spontaneous cure occurred in any considerable proportion of the cases, and at the earnest solicitation of these individuals many of whom would say "I had clavus last month and I will have it again next month" or "I have a breaking out of the buba every year," we made a practice of giving one or more injections of neo-salvarsan to patients in whose cases the history and examination satisfied us that they probably had had yaws.

The 127 cases which come under this heading may be tabulated as follows:

Diagnosis	No. of cases	Age in years		Duration in years	
		Average	Extremes	Average	Extremes
H	55	21.2	1-80	8.8 yrs.	2/12-50
H+	27	22.9	2-62	10.2 "	6/12-45
H ulceration ..	45	27.6	10-80	10.6 "	3/12-59

Of the cases in this group those designated H were without active lesions of any disease, but gave a satisfactory history of having had yaws. Under H+ we have grouped those individuals who, in addition to giving a history of having had yaws, had symptoms or signs of some other disease such as various skin eruptions, pains in various parts of the body, extensive scarring and other manifestations. One man gave a history of chancre and had a scar on the prepuce. The H ulceration group comprise 45 cases which in addition to a history of yaws showed active ulceration on some part of the body, usually old leg ulcers, which we could not definitely identify as yaws, and in most cases believed to be due to some other condition.

It seems not unlikely that this group of 127 individuals must have included many sufferers from latent yaws who, had they been left untreated, sooner or later would have again developed active lesions and not only suffered the disability arising from the disease themselves, but would also have become active agents in the spread of the disease. The statistics of this group seem to lend weight to this view. The average age in this group (23.8 yrs.) is lower than the average age of various other groups which showed active lesions, *e. g.*, groups MB, C+, CP, P, G, and G+. Moreover, the average duration in this group (9.7 years) is shorter than that in several groups showing active lesions, *e. g.*, C+, CP, P and G.

Indeed in 33, or 26 per cent, of these 127 cases the primary lesion had developed within 2 years prior to the time they applied for treatment. It seems highly probable that some of these 33 patients may have been in a free interval between the primary and secondary stages of the disease and that the majority of them were in a latent period following the early secondary eruption.

With a very limited time in which to work among a given population and with the object of accomplishing as much as possible toward eradicating the disease from the locality in which we were stationed, we think the policy of treating patients who gave a history of having had the disease, even though without active lesions at the time, is fully justified.

General Remarks

The *epitrochlear glands* were noted in 886 cases and were found to be palpably enlarged in 519, or 58.5 per cent; they varied in size from a grain of wheat to 1 or 2 cm. in diameter. Sometimes two or three glands, 1 cm. in diameter, were found in the epitrochlear region.

The *femoral glands* were noted in 121 cases and found enlarged in 100 per cent of the cases noted. In a majority of cases the femoral glands formed a visible ovoid swelling in Scarpa's triangle frequently attaining a width of 3 or 4 cm. and a length of 5 or 6 cm. It seems probable that the enlargement of this group of glands may have been due to the frequent pyogenic infections on the feet and legs that occur in a barefoot population.

The *spleen* was noted in 216 cases and found enlarged in 58, or 26.8 per cent. Malaria is common among the natives and may account for the large percentage of cases with splenic tumor.

The *Wassermann test* was made in 91 cases and found strongly positive in 78 cases (85.7 per cent), moderately positive in 4 cases, weakly positive in 1 case and negative in 8 cases.

The 8 cases with negative Wassermann reactions were distributed with reference to diagnosis as follows:

2	cases	diagnosed	B
1	"	"	C+
1	"	"	SL
1	"	"	H
1	"	"	H+
1	"	"	G
1	"	"	G+

The Wassermann test was repeated in a few cases after one or two treatments, the interval between the two tests being not over a few weeks. In no case did the result of the second test differ from that of the first. If it had been possible to perform the test at a longer interval after treatment, the results might have been different.

Thus it will be seen that in the small number of cases in which we have data on the Wassermann reaction the negative reactions all occurred in the late secondary stage, the tertiary stage, or in patients who had no active lesions but who gave a history of yaws.

SEQUENCE AND DURATION OF THE VARIOUS STAGES OF YAWS

In the discussion of this entire series of cases we have tried to take up the various distinctive manifestations of the disease in the order of their development. In so chronic a disease as yaws it was obviously impossible, in the limited time at our disposal, to observe a single case from the appearance of the madre buba, through the various stages, to the final deformity produced by the gummatous lesions. Moreover, it is apparent from the preceding sections that there is much overlapping of the various stages, many patients presenting two or even three different manifestations of the disease at the same time. In one case the madre buba persisted after the tertiary lesions had developed. Indeed, not being able to observe the sequence of events, we were often ignorant as to what it had been. We believe, however, that a statistical study of the data collected enables us to unravel this tangle. Accordingly, we have tabulated those cases that presented only a single manifestation of the disease, arranging them according to the average age of each group. The table also shows the extremes of age as well as the average and extremes of duration for each group.

Diagnosis	No. of cases	Age		Duration	
		Average	Extremes	Average	Extremes
M	15	6.6 yrs.	9/12-12 yrs.	2.3 mos.	1/12-7/12 yrs.
B'	82	8.8 "	1½-50 "	12.3 "	1/12-7 "
B	60	9.3 "	1-42 "	29.6 "	4/12-17 "
C 327		21.6 "	3-68 "	9 yrs.	4/12-58 "
H 127		23.8 "	1-80 "	9.7 "	2/12-59 "
P	5	25 "	15-45 "	14 "	10-19 "
SL	37	28.8 "	5-80 "	13.5 "	5/12-39 "
G	67	29.3 "	3-85 "	16.3 "	7/12-59 "
	720				

This series comprises 720 cases and the number included in a majority of the groups is large enough to give averages that are probably fairly reliable. It seems to us that this arrangement according to average ages probably indicates the sequence in which the various lesions develop. Confirmatory evidence in support of the correctness of this view is furnished by the fact that the average duration of the disease, at the time of observation, in the various groups, with one exception (Studded Lesions) follows the same orderly progression as do the ages. The fact that the extremes of age and duration in each group may vary widely does not, in our opinion, invalidate the deduction which we have just made.

We have attempted to use the data contained in the above table to answer certain other questions. It will be noted that the average ages and average durations are given as of the date of observation, and in the case of duration this does not represent the actual average duration of the disease or any particular stage of it. To illustrate: A patient in the primary stage of the disease may have given a history of having had the madre buba 2 months at the time he applied for treatment; it is quite possible that this lesion would, without interference, have persisted for another 2 months. Thus in that particular case the duration of the primary lesion would have been 4 months. If our reasoning is correct, the actual average duration of the madre buba may be estimated by determining the average duration of the lesions at the time of observation in a sufficiently large number of unselected cases under natural conditions and multiplying this average by two. Thus, in our series of madre cases, the average duration at the time of observation was 2.3 months, and if 15 cases were a sufficiently large number for generalization, we could say that the actual average duration of the madre stage of yaws is 4.6 months.

Furthermore, if one stage supervened promptly on the termination of the preceding stage, we could in turn calculate the actual average duration of each of the manifestations in the above series. For example, we would arrive at the average duration of the B' lesions by multiplying 12.3 months by 2 and subtracting the average duration of the madre stage. Thus we would find 20 months as the average duration of the florid secondary stage of the disease. The difficulty about applying such simple mathematical calculations to a disease like yaws is that there may be an interval free from active lesions and symptoms between the various stages of the disease, on the one hand, and, on the other hand, a considerable overlapping of the stages. This difficulty could have been overcome if it had been possible for us to obtain accurate histories of the date of onset of each stage of the disease. This we did not attempt, owing to the ignorance of a majority of the patients and the limited time at our disposal.

Although we obtained a history of the primary lesion persisting for 6 years in one case and saw patients with a florid secondary eruption, in one case 3 years, in another 7 years and in still another case 19 years after the onset of the disease, if we may accept the history given by these patients, it seems probable that the average duration of the florid secondary eruption is less than 2 years and that the late secondary lesions, especially clavus, may recur throughout a long period which, while frequently much longer, averages about 16 years and that in some cases patients may live to extreme old age, 85 years in one case in our series, with tertiary lesions.

RESULT OF TREATMENT

Neo-salvarsan was used in the treatment of the cases here reported. The drug was dissolved in freshly distilled water in the proportion of 0.1 gm. to 2 c. c. and injected within 30 to 45 minutes after being put in solution. The intravenous method was used in all cases except for young children with v ins difficult of access, these patients receiving the injections intra-muscularly in the buttock. The dose varied from 0.075 gr. for an infant under 1 year of age to 0.6 gm. for a fully developed adult. Intermediate doses were given in proportion to age and body weight. While reactions were frequent, including chill, fever, headache and general malaise, we observed no permanent ill effects and in none of the patients who received the intramuscular injections did we observe abscess formation which reached the surface, although some of them showed a painful brawny swelling.

It should be remembered that we were working under field conditions with no facilities for hospitalizing patients even over night, that many patients came two, three, and even four days journey on horse or on foot, over difficult trails, beaten

upon by tropical sun and often drenched by tropical rains, with the ground for a bed and the sky for shelter. Oftentimes within an hour after receiving an injection these patients started on the return journey to their distant homes again facing the hardships of the trail. The fact that no patient declined to return and receive further injections, when advised to do so, indicates as clearly as any statistics we might give either that the natives did not regard the reactions of a very serious nature or else that they considered the benefits to be derived as by far outweighing the discomforts of the reactions.

From a statistical standpoint the results of treatment in our series is of little value owing to the limited time over which the cases were observed and the fact that many patients received but a single treatment and were not seen again. The latter circumstance is easily explained. In the interior of Santo Domingo communication is largely by word of mouth and news spreads chiefly by means of the more or less chance wanderings of the natives. When we went up into the interior and set up our camp it was five days before the first patient, an old woman with "gomma," presented herself for treatment. Two days later three children with a florid secondary eruption were brought to us. During the next few days patients ventured in in small numbers, but when the news of the results obtained in the early cases treated began to spread, patients came in rapidly increasing numbers. By the end of the first month we were getting an average of about 25 to 30 new cases a day, and during the last two weeks of our stay the daily number of new and old cases ranged between 100 to 300. In spite of the fact that we sent out notices well in advance of our departure to stop new patients from coming in, the daily number increased almost up to the last day of our stay. Their appeal for help was so piteous and their condition so distressing that we could not refuse them a single injection, although we knew that we should never see them again. This accounts for the large number of cases in which we have no note as to the result of treatment.

It has been claimed that 90 per cent of yaws cases can be cured by a single injection of salvarsan. Our experience was not so favorable, though, if we had had a longer time in which to observe the results, we could have allowed a longer interval between injections and might have found it necessary to repeat the treatment in a smaller percentage of the cases. Moreover, the number of patients requiring more than one injection to effect a cure might have been fewer if 0.9 gr. of neo-salvarsan instead of 0.6 gm. had been adopted as the adult dose.

We have designated our results as cured, practically cured, much improved, improved, and unimproved. No patient was recorded as cured unless all the lesions (scars excepted) had entirely disappeared. If there remained at our last opportunity of observation only so much as a few black crusts almost ready to fall, where a week or two before there had been an abundant crop of fresh granulomata, we designated such cases as "practically cured" although we were convinced that could we have seen these patients a week later, without further treatment, they would have fallen into the cured list. The remaining designations, much improved, improved, and unimproved, are sufficiently clear without further comment, except to say that due conservatism was used in applying them and that, if error was made, it was probably on the side of underrating the actual improvement.

As to the ultimate results obtained we have no observations and even if the present condition of these patients could be ascertained, sufficient time has not elapsed to determine the permanence of the cures. We believe, however, that Ehrlich's ideal of "sterilizatio magna" is more nearly obtained with salvarsan or neo-salvarsan in yaws than in the treatment of any other disease.

There are obvious difficulties in giving a statistical statement of the results of treatment which can be correctly interpreted.

TABLE SHOWING RESULT OF TREATMENT IN 570 CASES

Diagnosis	Number of cases	Results		Cured				Practically cured				Much improved				Improved				Unimproved			
		No note	Noted	Number of doses				Number of doses				Number of doses				Number of doses				Number of doses			
				1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
M	15	4	11	2	..	..	..	5	2	1	..	..	1	..	..	..	..	..	..	..	..	..	..
MB′	25	10	15	2	2	..	..	4	1	..	..	6	..	..	..	..	..	..	..	..	..	..	..
MB′C	13	2	11	..	3	..	..	2	3	..	..	2	..	..	..	1	..	..	..	..	..	..	..
MB	6	3	3	..	..	..	..	..	..	..	..	1	..	1	..	1	..	..	..	..	..	..	..
MBC	5	3	2	..	1	..	..	..	..	..	..	..	..	..	..	..	1	..	..	..	..	..	..
B′	82	16	66	13	11	1	..	14	6	1	..	8	3	2	..	5	1	..	..	1	..	..	..
B′C	24	4	20	2	4	..	..	5	5	..	..	3	1	..	..	..	..	..	..	..	..	..	..
B	60	24	36	4	9	2	..	1	3	..	..	11	3	..	..	3	..	..	..	..	..	..	..
BC	106	26	80	..	10	1	..	7	6	..	..	36	7	1	..	7	3	1	..	1	..	..	..
BCP	13	7	6	..	3	..	..	..	..	..	..	3	..	..	..	..	..	..	..	..	..	..	..
C	327	143	184	5	5	5	1	3	9	..	..	27	16	..	..	55	10	..	..	41	7	..	..
C+	41	13	28	..	1	1	..	1	..	..	..	7	3	3	..	4	2	..	..	6	..	..	..
CP	50	15	35	..	..	1	..	..	1	1	..	5	7	..	..	10	1	..	..	9	..	..	..
P	5	3	2	..	..	..	..	..	..	..	..	1	..	..	..	1	..	..	..	..	..	..	..
SL	37	17	20	1	2	1	..	1	..	1	..	3	2	..	..	4	2	..	..	3	..	..	..
G	67	24	43	..	..	..	..	..	..	..	..	4	5	2	..	8	..	5	..	15	3	1	..
G+	12	4	8	..	..	..	..	..	..	..	..	4	1	..	..	1	..	..	..	2	..	..	..
	888	318	570	29	51	12	1	43	36	4	..	113	51	13	2	99	21	6	..	78	10	1	..
				93				83				179				126				89			

As previously stated, many of the cases which were designated as "practically cured" might have fallen into the "cured" column without further treatment, if there had been an opportunity for examing the patients after the lapse of another week. Moreover, the percentage of cures after one injection might have been materially increased, if we had allowed a longer interval of time in which to determine the result of the first injection.

The interval between injections was one week in the majority of cases; exceptionally it was as short as five days and in a moderate number of cases it was ten days or two weeks. The final result of treatment, as far as we had opportunity to observe it, was usually made one week after the last injection.

The above table gives the results of treatment in the various groups as noted at the last observation on each case and shows the number of injections each patient had received

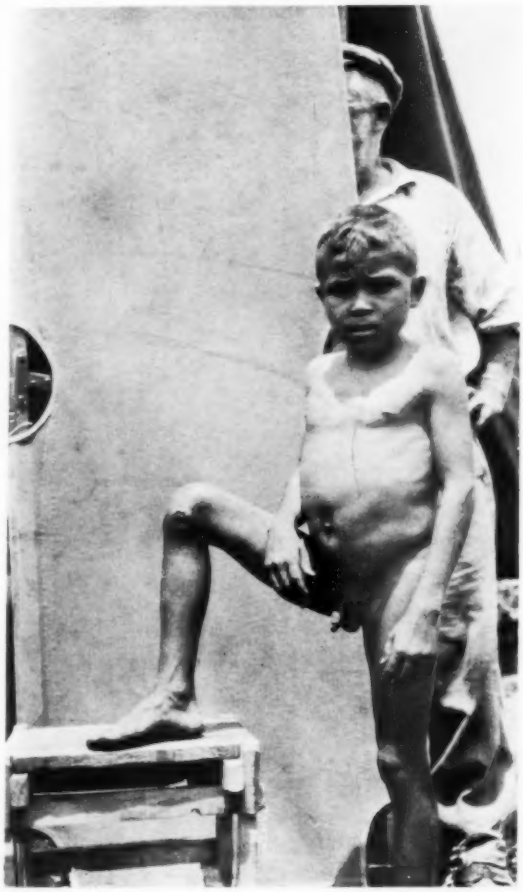


Fig.1

Fig.2

Fig.3 Primary Stage. Madre Buba or Mother Yaw.

Fig. 4

Fig. 5

Fig. 6

Fig. 7

Fig. 8

Secondary Stage. Figs. 4, 5, 6 and 8, Florid Secondary Eruption. Note Swelling of the Femoral Lymph-Glands in Fig. 5 and the Predilection for the Muco-Cutaneous Borders and Moist Surfaces in Figs. 7 and 8.

Fig. 9

Fig. 10

Fig. 11

Fig. 12

Secondary Stage. Figs. 9 and 10 show Granulomata of Unusual Size. Fig. 12 shows Circinate Arrangement of Lesions on Face, Giving the Indian War Paint Appearance.

Fig. 13

Fig. 14

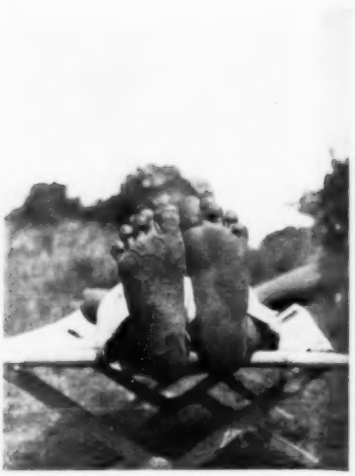


Fig. 15

Fig. 16

Fig. 17

Fig. 18

Late Secondary Stage. Figs. 13, 14, 15, 17 and 18 Clavus. Note the Fresh Granulomata on the Soles in Fig. 13, the Unilateral Involvement in Fig. 15, and the Marked Erosion in the Remaining Cases. Fig. 16 shows Marked Thickening of the Skin and Subcutaneous Tissues of the Feet, Probably a Rare, Late Manifestation of Yaws.

Fig. 19

Fig. 20

Fig. 21

Fig. 22

Fig. 19.—A "Yaws" Family. Fig. 20, "Studded Lesions." Fig. 21, Leucoderma Following "Studded Lesions." Fig. 22, Arthritis, Late Secondary Stage.

Fig.23

Fig.24

Fig.25

Fig.26

Tertiary Stage. "Gomma." Figs. 23 and 24. Indistinguishable Clinically from Syphilis.

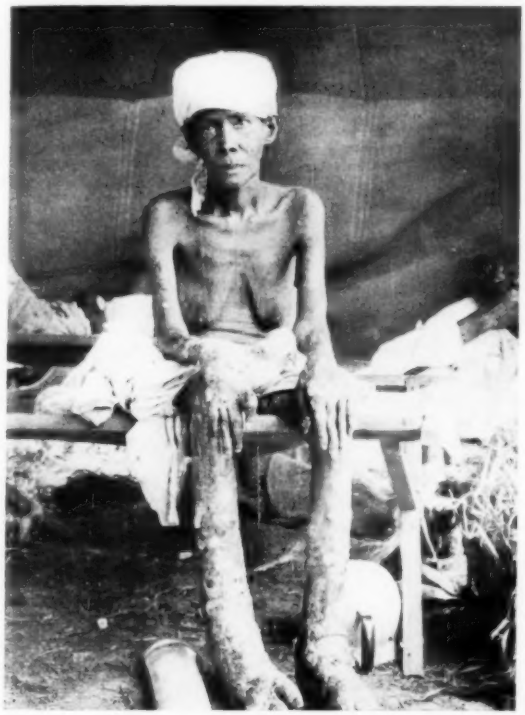


Fig. 27

Fig. 28

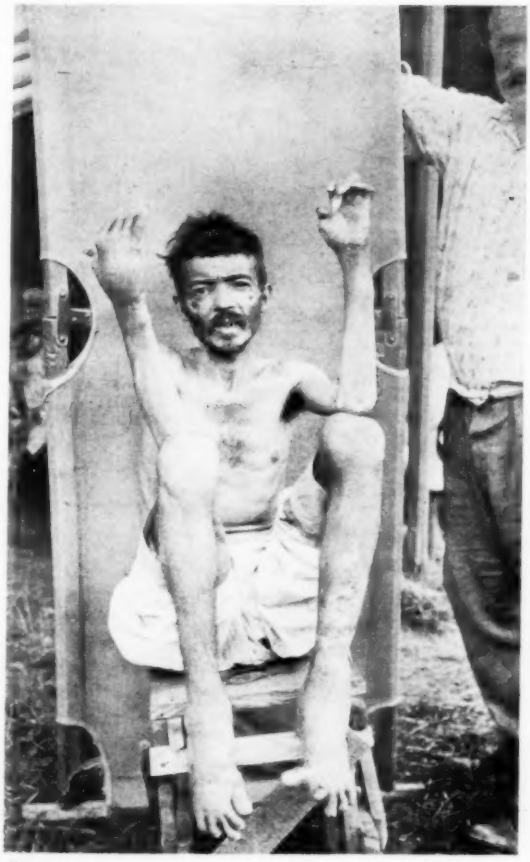


Fig 29

Fig. 30

Tertiary Stage. Fig. 28.—Bears Some Resemblance to Leprosy. Fig. 29.—Indistinguishable Clinically from Syphilis.

at the time of this note. The 127 patients who gave a history of having had yaws but who had no active lesions of the disease at the time they presented themselves for treatment are not included in this table, as we had no means of judging of the results of treatment in these cases. We have also excluded from the table 31 miscellaneous cases of yaws in which the results of treatment were difficult to determine owing to complicating diseases or for other reasons. Exclusive of these two groups there are 888 cases and in 570 of these we have notes as to the result of treatment.

Briefly summarized, irrespective of the number of injections each patient received, this table shows the following results:

	Cases	Approx.
Cured	93	16.32
Practically cured	83	14.56
Much improved	179	31.41
Improved	126	22.10
Unimproved	89	15.61
Total	570	100

There were 362 cases in the above series in which the final result noted was after a single injection of neo-salvarsan. Briefly summarized they are shown in the following table:

RESULTS AFTER A SINGLE INJECTION OF NEO-SALVARSAN

	Cases	Per cent
Cured	29	8.01
Practically cured	43	11.88
Much improved	113	31.21
Improved	99	27.34
Unimproved	78	21.54
Total	362	99.98

Perhaps one gets a better idea of the efficacy of treatment in yaws by considering the cases which showed no improvement following the administration of neo-salvarsan. In the above series of 570 cases only one patient (a gomma case) showed no improvement after three injections and only ten patients (3 gomma and 7 clavus cases) showed no improvement after two injections. This is certainly in marked contrast to the 113 cases which showed marked improvement after a single injection.

We have further analyzed our figures to see if they will show what stage of the disease is most readily amenable to treatment. For this purpose it seems probable that more reliable information will be obtained by combining the cured and practically cured groups and considering only those cases in which the result noted was obtained after a single injection. They are summarized in the following table:

Diagnosis	Total No. of cases	Average age in years	No. of cases Results noted	Cured or practically cured after one injection Number	Per cent
M	15	6.6	11	7	63.63
MB′	25	8.5	15	6	40.00
MB′C	13	11.6	11	2	18.18
MB	6	24.2	3	0	
MBC	5	10.0	2	0	
B′	82	8.8	66	27	40.91
B′C	24	12.9	20	7	35.00
B	60	9.3	36	5	13.88
BC	106	16.5	80	7	8.75
BCP	13	20.5	6	0	
C	327	21.6	184	8	4.34
C+	41	29.4	28	1	3.57
CP	50	32.7	35	0	
P	5	25.0	2	0	
SL	37	28.8	20	2	10.00
G	67	29.3	43	0	
G+	12	25.2	8	0	

The number of cases comprising some of the groups in the above table is too small to be of value for statistical purposes, but taken as a whole the figures seem to show what we would expect, *i. e.*, the earlier the stage, the more readily does it respond to treatment.

ACKNOWLEDGMENTS

We desire to express our appreciation of the courtesy and co-operation shown us during our stay in Santo Domingo by Rear Admiral Thomas Snowden, U. S. N., Military Governor, Commander Reynolds Hayden, M. C., U. S. N., Secretary of the Department of Sanitation and Beneficence, Lieutenant Commander Ralph M. Warfield, C. E. C., U. S. N., Secretary of the Department of Development, Public Works, etc., and to Mr. W. A. Elders, Administrator-General of the Santiago-Sanchez Railway.

We are deeply indebted to Dr. Stone and Mr. Hermann who acted as interpreters for us and whose intimate knowledge of the island and its inhabitants was of the greatest service.

To Mr. H. H. Raymond, President of the Clyde Steam Ship Company, we wish to make grateful acknowledgment for extending to the members of the commission and their equipment free transportation from New York to Santo Domingo and return.

JOHNS HOPKINS HOSPITAL BULLETIN

The Hospital Bulletin contains details of hospital and dispensary practice, abstracts of papers read and other proceedings of the Medical Society of the Hospital, reports of lectures, and other matters of general interest in connection with the work of the Hospital. It is issued monthly. Volume XXXIII is in progress. The subscription price is $4.00 per year.

(Foreign postage, 50 cents.) Price of cloth-bound volumes, $5.00 each.

A complete index to Vols. I-XVI of the Bulletin has been issued. Price 50 cents, bound in cloth.

STUDIES ON A CASE OF CHROMIC ACID NEPHRITIS

By Ralph H. Major

(From The Henry Ford Hospital, Detroit, Michigan)

A great deal of light has been shed upon the obscure points of kidney pathology by the newer studies on experimental nephritis. These observations have not only clarified many of our ideas about diseased kidney function, but have also contributed much to a clearer understanding of the complex and highly specialized functions of the kidneys in health.

In the production of experimental nephritis, chemical substances have been employed almost exclusively; arsenic, cantharidin, uranium nitrate, potassium bichromate, the tartrates and mercuric chloride being most frequently used. As the result of these studies we know that in a general way arsenic and cantharidin are glomerular poisons, while uranium, potassium bichromate, and the tartrates and mercury seem to have an especial affinity for the tubules. The more recent work, particularly that of MacNider,[10] has shown that, although a hard and fast line cannot be drawn, yet we are still justified on the basis of outspoken affinity in speaking of glomerular poisons and of tubular poisons.

The study of cases of poisoning from these chemicals that come into the hospital for treatment is important because of their relation to experimental nephritis. Corrosive sublimate has furnished the largest number of cases in this group. Lewis and Rivers[9] have published extensive chemical studies on a case of bichloride poisoning and have pointed out that, while the therapeutics of this condition have merited much attention in the literature, studies on the metabolism of these cases have been very meager and superficial. The number of other published cases of chemical nephroses is extremely small.

The following studies on a case of chromic acid poisoning are presented as a contribution to the subject of kidney pathology and particularly for comparison with the numerous observations in the literature on experimental chromate nephritis. This patient, suffering from an inoperable carcinoma of the face which had been treated by the application of chromic acid crystals, lived for four weeks after the development of the nephritis. During this period extensive studies of his blood and urine chemistry were carried out, marked variations from the normal were encountered and certain interesting changes brought about by therapeutic measures were noted. These observations have a certain interest as a study of the acidosis accompanying chromate nephritis and as a commentary on theories of renal secretion, particularly the "modern theory" of Cushny.[2]

Chromic acid was used as a cauterant as long ago as 1845 when Alexander Ure[23] described several cases of hemorrhoids treated with this agent. Marshall[17] in 1857 reported a series of cases of venereal warts in which the local application of an aqueous solution of chromic acid produced excellent results. Many similar reports appear in the literature during the succeeding years, although Gubler[4] in 1871 stated that "the absorption of chromic acid is not free from danger, as patients have been poisoned by a too extensive application to the surfaces of their bodies." J. William White[24] in 1889 reported the case of a young woman who died 27 hours after the local application of an aqueous solution of chromic acid to an extensive crop of venereal warts.

Industrial poisoning among workers in chrome plants from chromic acid has long been recognized. Pye,[15] in 1885, reported such cases and described the perforation of the nasal septum long known among workers as "chrome holes." He stated that the possession of such "chrome holes" is an object of pride to the workers, who often carry in their pockets a bent wire which they pass through the hole for the amusement of their friends.

Gergens,[3] in 1877, studied the toxic effect of chromic acid on rabbits and noted that it produced an acute nephritis. Kabierske,[7] in 1880, studied the pathological changes produced in the kidney by this chemical and Posner[21] continued and amplified these studies. Both Kabierske and Posner described in detail the exquisite tubular nephritis also. Kossa[8] observed that potassium chromate produced a hemorrhagic nephritis, but was interested particularly in the accompanying glycosuria which he described as "chromic acid diabetes." Viron[22] noted the frequent occurrence of both glycosuria and albuminuria in animals poisoned with chromate, but did not carry out any extensive pathological studies. Among later investigators who used the chromates for the purpose of studying experimental nephritis are Schlayer and Hedinger,[20] Heinike and Meyerstein,[5] Ophüls,[13] Hellin and Spiro,[6] Pearce Hill and Eisenbrey,[16] Weber,[25] Ruschaupt,[19] Austin and Eisenbrey[1] and MacNider.[11] These observers noted its particular though not exclusive affinity for the renal epithelium, and MacNider states that in the earliest stage there is a vascular injury followed rapidly by a tubular involvement which soon dominates the picture.

The patient upon whom these observations were made was a man of 59 and was suffering from a very extensive carcinoma of the left cheek which had been present for two years. This lesion, when first seen, involved almost the entire cheek, extending from the inner canthus of the left eye down upon the left half of the nose and thence down and over the cheek. The patient's mother had died of chronic nephritis, one brother had died of acute nephritis and another brother still living was suffering from chronic nephritis. The patient's urine was examined for the first time on December 8, 1920, and was normal in every respect, as was also a specimen examined on December 11, 1920. On December 11 the carcinoma was curetted and crystals of chromic acid applied until an eschar had formed. The urine, when examined on the following day, showed 4 gm. of albumin per liter. The amount of albumin

in the urine increased and three days later there were 7.3 gm. per liter, and hyaline and granular casts, red blood cells and numerous degenerated epithelial cells made their appearance.

On December 14, a little more than 48 hours following the application of the chromic acid crystals, the patient had an almost total suppression of urine and the blood urea was 60 mg. per 100 c. c. From this time on he waged an unsuccessful fight which terminated with his death on January 9, his blood urea on the day of his death reaching 340 mg. per 100 c. c. Many marked changes in his blood chemistry and in the excretion of fluids and solids took place. An intravenous phenolsulphonephthalein test was carried out on six occasions. On December 17, December 18, December 23 and on January 8 none was excreted, on December 27 and 31 the urine showed a faint unreadable trace. One gram of potassium iodide taken by mouth on January 30 was excreted in 24 hours. The McLean index which was determined every day varied from 0.01 to 0.47, the lowest values being at the onset of the nephritis and again towards the end.

A very marked feature of this case was the comparative well-being of the patient for more than two weeks following the appearance of the nephritis. During this period of 18 days he felt comparatively well except for some loss of appetite and occasional headaches, in spite of the fact that his kidneys were very severely damaged, his excretion of solids markedly diminished, and his blood urea soaring up around values ten times that of the normal high average. He was very impatient of the therapeutic measures, which consisted of forced fluid by mouth, saline purges, sodium bicarbonate administered by mouth, and rectal saline irrigations.

On December 28 his pulse became somewhat irregular and on December 31, 19 days after the onset of the nephritis, vomiting appeared which became increasingly frequent and was especially severe the last five days. His urinary output remained at a high level but sank very low the last five days, apparently because of the markedly lowered fluid intake. The patient never showed the slightest symptoms of uremia, no visible edema developed and the blood pressure varied from 145 to 110 systolic and 90 to 75 diastolic. He was given glucose intravenously, caffeine subcutaneously but gradually became weaker and weaker, the cardiac arrhythmia became more marked and he died on January 10, 30 days after the application of the chromic acid crystals.

At autopsy only the kidneys were removed. They measured 12 x 5 x 4.5 cm., the right kidney weighed 176 gm., the left 197 gm.; both were mottled in appearance, the cortex was swollen and the glomeruli were very indistinct. There was no free fluid in the abdominal cavity and no general anasarca.

Microscopically the kidneys showed extensive destruction of the tubular epithelium with debris in the lumen and marked swelling of many intact epithelial cells, the changes being especially marked in the convoluted tubules. There were a few mitotic figures seen in these cells, although the evidences of regeneration were not striking. Similar observations in experimental chromate nephritis were made by Kabierske (*l. c.*) and by many later investigators. The glomeruli were for the most part normal in appearance, although in some sections a few fibrosed glomeruli were seen. There were numerous areas of small-round-cell infiltration and much fibrosis in many places between the tubules. Because of the patient's age, it is doubtful just how much of the glomerular and interstitial fibrosis was due to the chromate. In general, the picture was that of a pure tubular nephritis.

A great deal of care was exercised in obtaining specimens and there is every reason to believe that no gross errors occurred that would materially affect the calculations. As the chemical studies were quite extensive, it is simpler to discuss each group separately.

METHODS

The non-proteid nitrogen, creatinin, creatin, uric acid and sugar determinations in the blood were carried out by the method of Folin and Wu. The blood urea was estimated by the method of Van Slyke and Cullen, blood amino acids by the method of Van Slyke, blood chlorides by the method of McLean, Van Slyke and Donleavy, blood calcium by the method of Halverson and Bergheim, phosphates by the method of Bloor.

The urine chlorides were determined by the method of Volhard and Arnold, the total nitrogen by the method of Folin and Farmer; creatinin, creatin and uric acid by the methods of Folin, Benedict and Myers and of Folin, and the urea by the method of Van Slyke and Cullen.

1. Fluid Exchange

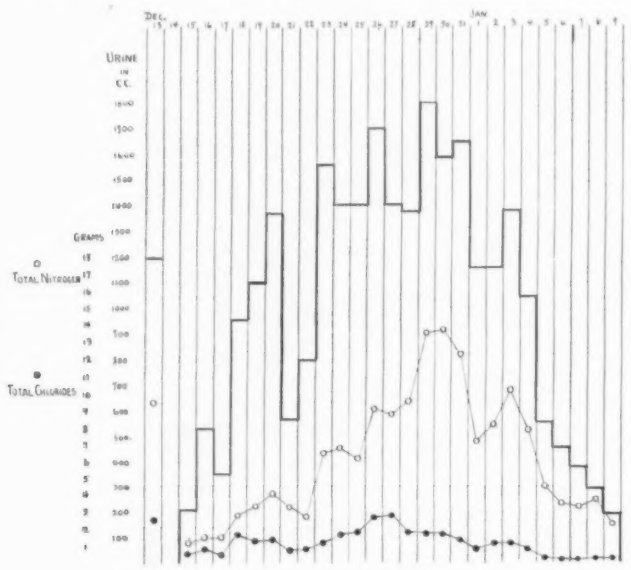
The observations on the fluid intake and output in this patient were quite complete and cover the entire of his stay in the hospital. The patient was urged at the onset of the nephritis to drink large amounts of water, which he did until a few days before death. No initial polyuria was observed such as has been described in the vascular reactions due to glomerular poisons. On the second day following the development of the nephritis, the urinary output was markedly reduced, falling to 10 c. c. Following the drinking of large amounts of water, the urinary output the following day again rose to 310 c. c., and there was a constant increase until the sixth day after the partial suppression. The total amount of urine excreted was 1360 c. c. During the period of lowered urinary excretion, the urine contained large amounts of albumin with numerous epithelial cells and epithelial casts—evidence of extensive tubular destruction. This suggests that the swelling of the tubular epithelium and choking of the tubules with debris may have caused the reduced urinary output, as observed by MacNider in experimental nephritis.

The urinary secretion remained uniformly high until four days before the death of the patient when it fell sharply reaching 280 c. c. the day before the patient died, this reduction corresponding in time to the period of continual vomiting with a marked diminution of fluid intake. The urinary record did not represent the entire fluid output, since the patient was purged constantly and considerable amounts of fluid were passed in this way. The specific gravity of the urine which

was 1.025 the day the nephritis appeared, afterward varied from 1.011 to 1.019, the average specific gravity, as determined by adding all the observations together and using their number as a divisor, being 1.014. The reaction of the urine was acid before any therapy was instituted, but following the administration of sodium bicarbonate became alkaline, becoming again acid whenever this therapy was discontinued.

2. Total Nitrogen and Chloride Excretion

The total nitrogen, non-proteid nitrogen and chloride excretion fell very sharply following the onset of nephritis reaching the low level of 1.17 gm., .96 gm. and .59 gm., respectively. This marked depression persisted for four days and then was followed by a slow and gradual rise, until ten days after this depression the patient excreted 13.5 gm. of total nitrogen,



Curve 1.

13.4 gm. of nonproteid nitrogen and 1.62 gm. of chlorides in 24 hours. Similar curves of nitrogen excretion were observed by Pearce, Hill and Eisenbrey, by Green, and by Austin and Eisenbrey in experimental chromate nephritis. If this curve of nitrogen and chloride is super-imposed on a curve of the fluid output, it will be seen that the two follow each other closely. The nitrogen output is reduced, the chloride output is markedly reduced, yet their fluctuations correspond closely to those of the urinary secretion.

3. Urea

The urea nitrogen excretion was constantly low. The first determination made after the onset of nephritis showed a total 24 output of 6.32 gm. On December 15, the day following the marked suppression of urine, it fell to 0.81 gm. and on the following day it was only 1.2 gm. It later rose slowly, reaching the highest level on December 29 when it was 9.49 gm. During the last five days of the patient's illness it again showed a decided depression, falling to 1.62 gm. on the day before the patient's death. In comparing these figures with those of the total nitrogen and non-proteid nitrogen excretion, it is seen that, while these two are markedly diminished, yet their depression is not relatively so great as that of the urea excretion.

The blood urea, on the other hand, was high at the onset—65.38 gm. on December 14, and afterwards showed a constant and gradual rise, reaching the high value of 340 mg. per 100 c. c. the day before death. For two weeks from December 2 to January 3, during the period when the patient, as previously mentioned, felt comparatively well, the blood urea varied from 168 to 227 mg.

These urea values are interesting in the light of Cushny's well-known, modern theory. Cushny states that "the modern view requires that the urea, like the other constituents of the urine, pass out by the capsule." He cites, in proof of this view, that the excretion of urea ceases at the same time as the secretion of water by the kidney. In this patient, however, the secretion of water, after an initial drop, rose rapidly and continued at a high level while the urea output remained very low and the blood urea continued to increase markedly.

Urea curves similar to that in this case have been frequently noted in cases of chronic diffuse nephritis showing at autopsy both glomerular and tubular lesions. Such urea values, as noted in our case of tubular nephritis, raise the question whether the older view, that urea is excreted mainly by the tubules, does not explain the picture better than the modern theory.

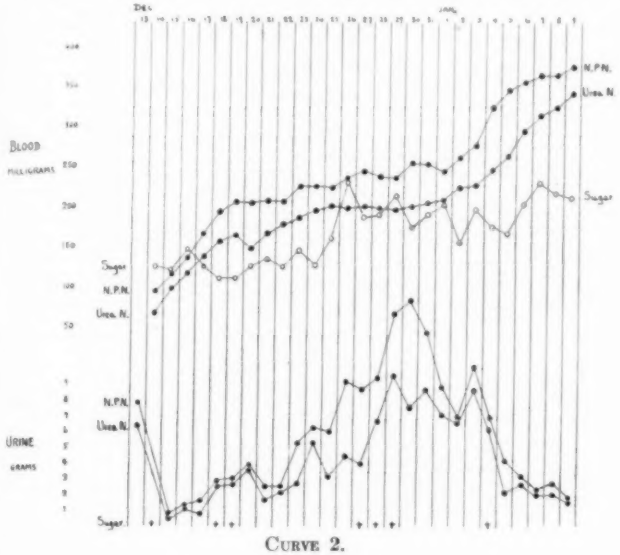
Further evidence in favor of this older view is found in the work of Oliver.[14] This observer, working with xanthydrol, which produces a characteristic crystalline product with urea, found evidence of urea excretion in both the glomeruli and tubules. The marked diminution of urea excretion in our case of chromium nephritis would indicate that a part of the urea may have escaped through the intact glomeruli, while still another fraction may have been secreted by such portions of the tubular epithelium as were not destroyed.

4. Creatinin and Creatin

The 24 hour excretion of creatinin fell to 0.23 gm. two days after the onset of nephritis, but following this rose gradually to normal and hovered about 1 gm. for two weeks. The last few days it was again depressed, falling to 0.3 gm. the day before death.

The blood creatinin on the other hand was 4.56 gm. on December 14 and rose rapidly until the fifth day after the onset of the nephritis when it reached 14.8 mg. per 100 c. c. From this time to the end it showed a gradual rise, reaching 17 mg. the day before death. Here again the patient although comparatively free from symptoms for two weeks, showed blood creatinin values varying from 13.68 mg. to 15.68 mg. per 100 c. c., demonstrating the point emphasized particularly by Myers and Lough[15] that values above 5 mg. indicate an early fatal termination and also that a progressive increase in blood creatinin is a sign of unfavorable prognostic import.

The blood creatin was increased to 12.48 mg. per 100 c. c. on the day following the partial suppression of urine and on the next day fell sharply to 5 mg. It remained about this

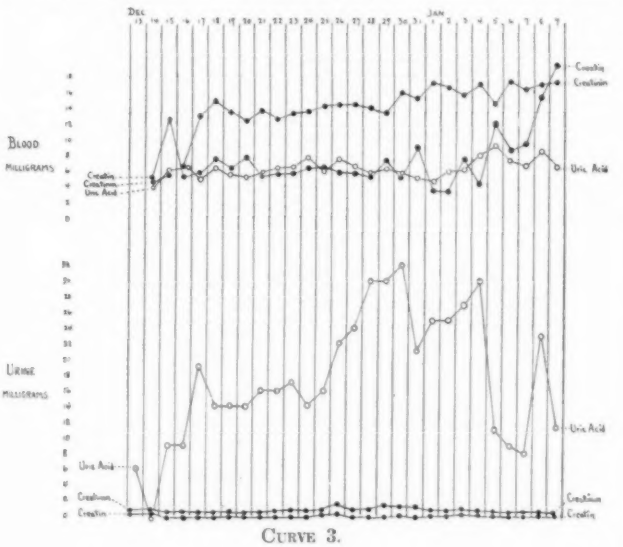


CURVE 2.

latter level until a few days before death when it rose abruptly, reaching 18.72 mg. per 100 c. c. on the day before death. The excretion of creatin varied from 0 to .17 mg.

5. URIC ACID

The blood uric acid values were constantly high, varying from 4 mg. per 100 c. c. on December 14, the second day of the nephritis, to 9.15 mg. on January 5. There was not the



CURVE 3.

same striking increase in blood uric acid as there was in the blood urea, although the amounts were increased, the average reading being 6 mg. per 100 c. c. The uric acid excretion was consistently low varying from 6 mg. to 30 mg. in 24 hours. This patient was on a very low purine diet and the determinations show a very definite uric acid retention, which does not seem in complete harmony with the theory of Cushny which postulates a glomerular excretion of uric acid.

6. CHLORIDES

The plasma chlorides in this case of chromic acid nephritis show a consistently low level varying from 378 mg. to 558 mg. per 100 c. c. following the development of the kidney lesion. The total chlorides in the urine were even more markedly lowered, varying from .1 gm. to 2.76 gm. in 24 hours. No marked fluctuations were observed, although the general tendency was a gradual lowering in the amount excreted as the process continued. The low values were doubtless due in part to the low chloride content of the diet, and the absence of any increase in the plasma chlorides in the presence of an extensive tubular nephritis would seem to be evidence in favor of the excretion of these substances by the glomeruli.

7. SUGAR

The urine of this patient frequently showed traces of sugar which apparently bore no relation to amount of blood sugar present. The urine during the first 12 days showed traces of sugar on three occasions, although the blood sugar was not higher than 159 mg. per 100 c. c. The last four days of the patient's illness the blood sugar varied from 204 mg. to 229 mg. but with no glycosuria. Intravenous injections of glucose given on three occasions produced no marked change in the blood sugar curve.

Kossa (*l. c.*) in experimental chromate nephritis noted glycosuria in the absence of a hyperglycemia and explained this phenomenon by the assumption of an increased glomerular permeability. Cushny has attacked this theory of increased glomerular permeability used so long in phloridzin glycosuria, and has pointed out that a failure on the part of the tubular epithelium to re-absorb the excess of glucose excreted by the glomerulus explains the phenomenon equally well or better. In chromic acid nephritis with extensive tubular necrosis, such a failure of reabsorption is presumably present.

8. CARBON DIOXIDE, ACETONE, PHOSPHATES AND AMINO ACIDS

Evidence of acidosis in this patient was present soon after the onset of nephritis, the carbon dioxide tension in the plasma on December 15 falling to 37 per cent. The patient was immediately given sodium bicarbonate by mouth with the result that there was a sharp rise to 64 per cent the following day. As the result of such alkali therapy a normal carbon dioxide tension was maintained until the onset of vomiting when the tension fell to 30 per cent, and did not later rise above 37 per cent.

Acetone was present in the urine the last ten days, although it was absent in the early stages in spite of other evidence of acidosis. Determinations of inorganic phosphates in the blood were made on four occasions, showing 35 mg. per 100 c. c.

SUMMARY OF CHEMICAL STUDIES IN CHROMIC ACID NEPHRITIS

Blood milligrams per 100 c. c.

	December																		January									
	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	1	2	3	4	5	6	7	8	9	10
Non proteid nitrogen	..	91.	123	137	165	191	204	202	205	205	224	221	222	234	241	238	233	253	252	242	260	277	321	343	355	364	364	373	....
Urea nitrogen	..	65.	93	118	136	155	162	148	168	179	184	194	200	198	201	199	195	199	204	209	222	227	246	261	295	311	322	340	....
Creatinin	..	4.5	5	6	13	15	13	12	14	13	13	13	14	14	14	14	14	16	15	17	17	16	17	15	18	17	17	17	....
Creatin	..	5.	12	5	6	8	6	8	5	5	6	6	6	6	6	5	7	5	9	3	3	8	4	12	9	9	15	19	....
Uric acid	..	4	6	7	5	6	6	5	6	6	3.6	8	68	7	7	5	6	5	5	5	6	6	8	9	7	7	9	6	....
Plasma chlorides	..	730	558	468	450	..	400	390	378	383	378	405	405	445	470	470	440	460	480	522	475	450	485	438	440	407	423	405	....
Sugar	..	123	122	144	123	110	110	124	132	122	142	125	160	231	187	190	211	173	191	203	155	198	174	168	204	230	217	210	....
CO_2 in per cent	..	..	37	64	50	..	52	62	70	62	53	48	49	52	45	45	40	44	43	40	42	36	30	37	34	32	31	32	....
H-ion serum ph	..	..	..	..	....	..	..	....	....	..	....	....	..	..	....	....	..	..	....	....	....	....	7.6	....	....	..	....	7.7	....
Calcium	..	..	..	..	....	..	..	....	....	..	....	7.2	..	..	....	....	..	9.3	....	9.9	....	....	....	....	....	8.2	....	....	....
Inorganic phosphates	..	..	..	..	....	..	..	....	....	..	....	....	..	..	....	....	35	..	32	....	....	....	....	....	....	39	50	....	....
Total phosphates	..	..	..	..	....	..	..	38	....	38	....	....	..	..	....	....	..	..	....	....	....	....	....	....	....	..	....	....	....
Amino acids	..	..	..	..	....	..	..	....	....	..	....	....	..	..	....	....	..	12.7	..	..	....	....	....	....	....	..	32	34	31

Urine output

Fluid intake	..	480	2980	3430	2880	3740	2770	2890	2480	3230	1140	1850	1720	1872	2252	2390	2502	2465	2570	2570	2310	1840	1640	1855	795	992	1180	550	1854
Total urine	1200	10	310	530	520	950	1100	1360	560	800	1555	1400	1400	1700	1400	1375	1800	1580	1640	1150	1150	1370	1010	560	455	370	435	280	175
Specific gravity	1025	1	1016	1013	1013	1013	1011	1012	1011	1012	1013	1015	1012	1014	1016	1015	1016	1014	1015	1016	1016	1015	1017	1019	1017	1017	1017	1019	1019
Albumin	6.9	..	7.3	.7	+++	.7	++	+++	+++	.8	+++	+++	+	+	+++	+++	.8	.8	+++	+++	+++	+++	+++	+++	+++	2.	+++	+++	+++
Total nitrogen	9.65	..	1.17	1.53	1.56	2.85	3.39	4.08	3.40	2.87	6.50	6.83	6.2	9.18	8.82	9.60	13.5	14.2	12.3	7.28	8.25	10.2	7.91	4.55	3.49	3.25	3.89	2.31	1.24
Non proteid nitrogen	7.70	..	.96	1.45	1.46	2.8	3.	3.95	2.5	2.5	5.3	6.29	6.	9.1	8.7	9.4	13.4	14.1	12.1	....	6.8	10.1	6.98	4.15	3.29	2.29	2.65	1.8	....
Urea nitrogen	6.32	..	.8	1.2	.83	2.57	2.64	3.77	1.68	2.28	2.6	5.38	3.22	4.51	3.96	6.60	9.49	7.49	8.65	6.99	6.85	8.58	6.12	2.21	2.81	2.22	2.07	1.62	.73
Ammonia nitrogen	.31	..	.02	0.16	.31	.17	.04	.01	.01	.2	.55	.62	.70	.76	.70	.34	.74	.17	0.17	0.67	.59	.82	.84	.07	.55	.52	.44	.36	.15
Creatinin	.8	..	.23	.32	.28	.48	.33	.45	.18	.3	.72	.57	.84	1.1	.88	.96	1.2	1.07	1.9	.79	.79	1.0	.80	.45	.39	.37	.39	.30	.2
Creatin	.17	..	.02	0	0	0	.07	.05	.04	0	0	.1	.02	.02	0	0	0	.07	0	.13	.13	.27	.38	.02	.18	.05	.18	.04	.01
Uric acid	.6	..	0	9.	19.	14	14	14	16	16	17	14	16	23	24	30	30	32	21	25	25	27	30	11	9	8	23	12	39
Total chlorides	2.5	..	.59	.79	.52	1.14	1.21	1.56	.73	.80	1.24	1.68	1.82	2.72	2.76	1.68	1.62	1.74	1.31	.81	1.11	1.10	.76	.22	.14	.22	.26	.20	.71
H-ion	6.8	..	5.8	9.	9.	8.7	7.8	8.	8.2	8.2	7.9	8.5	9.	8.4	8.5	8.5	8.8	8.6	9.2	9.2	9.2	9.2	9.2	8.8	9.0	8.8	8.7	8.5	7.8
Sugar	..	+	..	..	....	+	+	....	....	..	....	....	..	..	+	+	+	..	....	....	....	....	+	....	....	..	....	....	....
Phosphates as P_2O_5	.9	..	.05	.13	.13	.25	.44	.68	.28	.88	1.68	1.12	1.22	1.3	....	1.15	..	1.12	....	1.14	1.14	1.34	1	.63	.45	.34	.38	.1	.03
Chromium	+	..	..	..	....	..	..	....	....	+	....	....	..	..	....	....	..	+	+	....	....	....	....	....	....	....	..	....	....	....
Acetone	..	..	..	..	....	..	..	....	....	..	....	+	..	..	....	+	..	+	+	+	+	+	+	+	+	+	+	+	+
McLean Index	..	..	.13	.12	.05	.09	.13	.14	.09	.08	.09	....	.11	.17	.14	.3	.47	.35	.38	.34	.29	.37	.21	.06	.07	.04	.01	.01	....

Albumin, total nitrogen, non-proteid nitrogen, urea, ammonia and total chlorides in grams.
Creatinin, creatin, uric acid and phosphates in milligrams.

FIG. 1.—Microphotograph of the kidney showing desquamation of the tubules, interstitial fibrosis and areas of small, round cell infiltration. (Hematoxylin and eosin. Bausch and Lomb obj. 4 oc. × 10.)

FIG. 2.—Microphotograph of the kidney showing extensive tubular desquamation with an intact glomerulus. (Hematoxylin and eosin. Bausch and Lomb obj. 4 oc. × 10.)

on December 29 and 50 mg. per 100 c. c. on January 8, two days before death. The phosphate excretion in the urine was consistently low, falling to 0.1 gm. the day before death. These findings indicate an early phosphate acidosis complicated later by an acidosis of acetone body origin. Determinations of the blood amino acids were made on four occasions and showed high values, 12.7 mg. per 100 c. c. on December 30, 1920, 32 mg. on January 7, 1921, 24 mg. on January 8 and 31.3 mg. on January 9.

CONCLUSIONS

In this case of chromic acid nephritis the kidney lesion present was that of a pure tubular nephritis. No edema was noted clinically and no anasarca or ascites was present at autopsy. No symptoms of uremia were present, and the patient, during the greater part of his illness, felt comparatively well.

The urine output following a temporary depression was high, but the urine itself was of low specific gravity and the excretion of nitrogen, chlorides, phosphate, creatinin, uric acid and urea was markedly diminished. Glycosuria appeared from time to time but it bore no apparent relationship to the amounts of blood sugar present.

A study of the blood chemistry showed very high values for urea, inorganic phosphates, amino acids and creatinin and values higher than normal for uric acid. Determinations of the carbon dioxide content of the blood plasma showed definite evidence of acidosis which responded promptly to alkali therapy.

In conclusion it is a very great pleasure to acknowledge the assistance of Dr. R. L. Haden, under whose direction the chemical studies were carried out.

BIBLIOGRAPHY

1. Austin, J. H., and Eisenbrey, A. R.: Experimental Acute Nephritis: The Elimination of Nitrogen and Chlorides as compared with that of Phenolsulphonephthalein. J. Exper. Med., 1911, XIV, 366.

2. Cushny, A. R.: The Secretion of the Urine, London, 1917.

3. Gergens, E.: Beobachtungen ueber die toxische Wirkung der Chromsäure. Arch. f. exper. Path. u. Pharmakol, 1877, VI, 148.

4. Gubler: Quoted by White (*l. c.*).

5. Heinike, A., and Meyerstein, W.: Experimentelle Untersuchungen ueber den Hydrops bei Nierenkrankheiten. Deutsches Arch. f. klin. Med., 1907, XC, 101.

6. Hellin, Dionys, and Spiro, Karl: Ueber Diurese. Arch. f. exper. Path. u. Pharmakol., 1897, XXXVIII, 368.

7. Kabierske, Eugen: Die Chromniere. Inaug. Dissertation, Breslau, 1880.

8. Kossa, Julius: Ueber Chromsäure-Diabetes. Arch. f. d. ges. Physiol., 1902, LXXXVIII, 627.

9. Lewis, D. Sclater, and Rivers, T. M.: Chemical Studies on a Case of Bichloride Poisoning. John Hopkins Hosp. Bull., 1916, XXVII, 193.

10. MacNider, William deB: A Study of the Renal Epithelium in Various Types of Acute Experimental Nephritis. J. Med. Research, 1912, XXVI, 79.

11. MacNider, Wm. deB.: A Study of the Renal Epithelium in Various Types of Acute Experimental Nephritis and of the Relation which exists between the Epithelial Change and the total Output of Urine. J. Med. Research, 1912, XXVI, 79.

12. Marshall: The Application of a Solution of Chromic Acid as a new Stimulant Escharotic in Warts and other Growths. Lancet, 1857, I, 88.

13. Myers, Victor C., and Lough, Walter G.: The Creatinin of the Blood in Nephritis, Its Diagnostic Value. Arch. Int. Med., 1915, XVI, 536.

14. Oliver, Jean: Mechanism of Urea Excretion. J. Exper. Med., 1921, XXXIII, 177.

15. Ophüls, W.: Some Interesting Points in regard to Experimental Nephritis. J. Med. Research, 1908, XVIII, 497.

16. Pearce, R. M., Hill, M. C., Eisenbrey, A. R.: Experimental Acute Nephritis: The Vascular Reactions and the Elimination of Nitrogen. J. Exper. Med., 1910, XII, 196.

17. Posner, Carl: Studien ueber pathologische Exsudatbildungen. Virchows Arch. f. Path. Anat., 1880, LXXIX, 311.

18. Pye, Walter: On the Local Lesions Caused by the Alkaline Salts of Chromic Acid. Ann. Sur., 1885, I, 303.

19. Ruschaupt, W.: Beiträge zur Diurese. Arch. f. d. ges. Physiol., 1902, XCI, 595.

20. Schlayer and Hedinger: Experimentelle Studien ueber Toxische Nephritis. Deutsches Arch. f. klin. Med., 1907, XC, I.

21. Ure, Alexander (Quoted by Ernest Hart): Lancet, 1857, I, 543.

22. Viron, L.: Contribution à l'étude physiologique et toxicologique de quelques préparations chromées. Thèse de Paris, 1885.

23. Weber, S.: Experimentelle Untersuchungen zur Physiologie und Pathologie der Nierenfunktionen. Arch. f. exper. Path. u. Pharmakol., 1906, LIV, I.

ADAPTATION OF BACTERIA TO GROWTH ON HUMAN MUCOUS MEMBRANES WITH SPECIAL REFERENCE TO THE THROAT FLORA OF INFANTS

By ARTHUR L. BLOOMFIELD

(From the Biological Division of the Medical Clinic, The Johns Hopkins University and Hospital)

In studying the problem of respiratory infection it soon became apparent that certain fundamental data in regard to growth and colonization of bacteria in the upper air passages must be assembled before real progress could be made. It has seemed advisable, therefore, to digress from the original practical problem to more purely biological questions of growth adaptation of bacteria on the respiratory mucous membranes. The recent trend of bacteriological study clearly indicates that the conditions allowing and promoting the growth of microorganisms are vastly more complex than the early investigators in this domain were led to believe. The newer studies on the importance of hydrogen-ion concentration, and of growth accessory substances in particular, have opened roads which will undoubtedly lead into very extensive and prolific fields of

research. However, these considerations apply more especially to growth of bacteria on artificial nutritive media, and the facts at hand help but little in elucidating the conditions of growth of micro-organisms in the body. It seems that factors more elusive than those of acid-base equilibrium and such matters govern the actual conditions of human parasitism. To illustrate—while the pneumococcus is found in the mouths of approximately 50 per cent of normal people, we find that the pH of the mouth secretions is almost always greater than that which would allow the initiation of growth of the pneumococcus in the test-tube.[1] Furthermore, certain organisms such as *B. coli* and Friedländer's bacilli, whose growth requirements *in vitro* are simple, do not colonize on the mucous membranes of the upper air passages, whereas more fastidious organisms such as streptococci are invariably present. It is apparent, therefore, that one cannot directly apply test-tube criteria in explaining growth on human mucous membranes.

The immediate question under consideration, then, concerns the factors which allow growth of certain organisms in the upper air passages and prevent that of others. In a previous study it was pointed out that the bacteria found in the throat considered from this standpoint fall into several distinct groups.[2] There is in the adult (with aërobic methods) a constant habitual flora consisting of non-hemolytic streptococci, Gram-negative cocci, and diphtheroids. These organisms are found widely disseminated through the mouth cavity—on tongue, tonsils, and pharynx. They occur in normal and in sick people, in those with foci of infection, and in those whose tonsils have been removed. All the evidence indicates that they grow free on the normal mucous surfaces. In distinction to this group we find another comprising for the most part potentially pathogenic organisms. These are usually localized in some definite area of infection such as the tonsil, adenoid, or a sinus, or they may occur temporarily and sporadically on the free surfaces of the mucous membranes—evidently transients which have not actually colonized. What then are the conditions which create such a sharp and fundamental difference between these two groups of organisms? An analysis of the known facts in regard to test-tube growth requirements of the two groups does not answer this question. For example, hemolytic streptococci are no more fastidious than many of the green-producing strains, and yet the former are not members of the normal habitual flora, whereas the latter are constantly present. It seems to us necessary to fall back on a theory of adaptive parasitism, without attempting to define the exact chemical conditions involved. In other words, is it possible that the non-hemolytic streptococci gradually—perhaps during a period of thousands of years—became adapted to growth on human mucous membranes, while other bacteria show a total absence of such adaptation or only partial and abortive degrees?

It seemed that some information about this question might be gleaned from a study of the development of the throat flora in infants. Such individuals would furnish a most desirable experimental material for the following reasons: First, one would be dealing with a virgin soil not previously the habitat of any bacteria. Secondly, no local foci of infection such as diseased tonsils or sinuses are present to obscure the bacteriological picture. Thirdly, the teeth with their associated collections of food particles in which organisms of various sorts may breed have not yet appeared. If it should turn out that any particular varieties of organisms appeared early, regularly, and in large numbers, one might reasonably assume that such organisms possessed a high degree of inherent adaptation to growth in these regions. The present paper concerns itself, therefore, with a study of the throat flora of infants.

Literature

No attempt will be made to review the extensive literature on the bacteriology of the mouth. Our work concerns itself with defining the position of certain well-known organisms rather than with enumerating all bacteria which may be recovered from the upper air passages under all conditions. Brailovsky-Lounkevitch [3] has reviewed the literature on the bacteriology of the mouth in infants. She, as well as other observers, has found no organisms during the first few hours of life but notes their rapid appearance after the twelfth hour. Beyond this important observation, however, we find little but a general catalogue of organisms without information which would indicate their significance.

Methods

Through the courtesy of the staff of the Obstetrical Department it was possible to examine infants shortly after birth and at more or less regular intervals thereafter. A swab was passed over the palate and pharynx and plated on rabbit blood agar and oleate hemoglobin agar according to the method described elsewhere.[4] Care was taken to secure a good spread of colonies and careful qualitative and quantitative observations were made of the various bacteria present. A note was made of the relation of the culture to the time of nursing.

Results

The results are presented in Table I. The first fact of importance is that the cultures made very shortly after birth—under 12 hours, and before the baby had nursed—were sterile. This was so in seven cases (I, V, IX, XI, XII, XIV, XIX). In Case XVII a culture made three hours after birth and before nursing yielded four colonies of staphylococcus albus and two colonies of a diphtheroid. From the twelfth hour on (at which time nursing began) organisms were uniformly present in large numbers. In Case VII a culture made at 12 hours, but before nursing, showed a few white staphylococci and several hundred green streptococci. The above findings confirm those of previous observers.

A few words may now be said about each of the organisms encountered in later cultures.

1. *Staphylococci (albi).*—White staphylococci were present in over half of the cultures but were not a constant finding. They varied in number in various cultures from a few to innumerable colonies. Many types, both hemolytic and non-

TABLE I

RESULTS OF THROAT CULTURES FROM INFANTS[1]

	Aug. 6—*æt.* 11 hrs. (has not nursed)	Aug. 8—*æt.* 3 days	Aug. 15—*æt.* 10 days	Aug. 17—*æt.* 12 days
Case I—F.....	No growth	Staph. albus 20 Tetragenus a few *Strept. (green)* *∝ *Strept. (grey)* ∝	Staph. albus ∝ Tetragenus a few *Strept. (green)* many *Strept. (grey)* ∝ Staph. aureus 50	Staph. albus ∞ *Strept. (green)* ∞ *Strept. (grey)* ∞
	Aug. 8—*æt.* 14 hrs. (has nursed)	Aug. 9—*æt.* 2 days	Aug. 15—*æt.* 8 days	Aug. 17—*æt.* 10 days
Case II—E....	Tetragenus 1 Gram+ diphtheroid 1	Tetragenus many Gram-neg. cocci many *Strept. (green)* ∝ *Strept. (grey)* a few	Tetragenus ∝ *Strept. (green)* ∝ *Strept. (grey)* many Staph. albus 50	Tetragenus many *Strept. (green)* many *Strept. (grey)* ∞ Staph. albus few
	Aug. 8—*æt.* 16 hrs. (has nursed)	Aug. 9—*æt.* 2 days	Aug. 10—*æt.* 10 days	Aug. 15—*æt.* 8 days (culture while nursing)
Case III—R...	Staph. albus 16	Spreaders	Tetragenus sev. hundred *Strept. (green)* many *Strept. (grey)* ∝	Staph. albus sev. hundred Tetragenus few *Strept. (green)* ∞ *Strept. (grey)* ∞ Staph. aureus 5
	Aug. 9—*æt.* 14 hrs. (has nursed)	Aug. 10—*æt.* 2 days	Aug. 15—*æt.* 7 days	Aug. 19—*æt.* 11 days
Case IV—Fr...	Staph. albus 200 *Strept. (green)* a few *Strept. (grey)* many	Staph. albus many *Strept. (green)* ∞ *Strept. (grey)* ∞ Tetragenus ∞	*Strept. (green)* ∞ *Strept. (grey)* a few Tetragenus ∞	Staph. albus many *Strept. (green)* ∞ *Strept. (grey)* many Tetragenus many Staph. aureus few
	Aug. 23—*æt.* 16 hrs. (has nursed)	Aug. 24—*æt.* 1½ days	Aug. 26—*æt.* 4 days	
Case V—O.....	Staph. albus 100 *Strept. (grey)* 50	Staph. albus 120 Gram+ coccus many Tetragenus ∞	Staph. albus few *Strept. (grey)* *Strept. (green)* many Tetragenus many Staph. aureus a few Gram+ bacillus 6	
	Aug. 1—*æt.* 7 hrs. (has not nursed)	Aug. 2—*æt.* 30 hours	Aug. 5—*æt.* 3 days	Aug. 8—*æt.* 6 days
Case VI—S....	No growth	Staph. albus 300 Tetragenus a few *Strept. (green)* many Gram-neg. bacillus ∞	Staph. albus sev. hundred Tetragenus a few *Strept. (green)* ∞	Staph. albus sev. hundred Tetragenus a few *Strept. (green)* sev. hundred *Strept. (grey)* ∞ Staph. aureus 12
	Aug. 2—*æt.* 12 hrs. (has not nursed)	Aug. 3 *æt.* 31 hours	Aug. 5—*æt.* 3 days	Aug. 8—*æt.* 6 days
Case VII—J...	Staph. albus few *Strept. (green)* sev. hundred	Staph. albus few *Strept. (green)* ∞ *Strept. (grey)* ∞ Gram-neg. cocci few	Staph. albus ∞ *Strept. (grey)* few	Staph. albus ∞ *Strept. (grey)* few
	Aug. 3—*æt.* 22 hrs. (has nursed)	Aug. 5—*æt.* 3 days	Aug. 9—*æt.* 7 days	Aug. 12—*æt.* 10 days
Case VIII—Sn.	Staph. albus ∝ *Strept. (green)* many *Strept. (grey)* many	*Strept. (green)* ∝ Tetragenus ∝ Gram+ diphtheroid few	*Strept. (green)* ∞ Tetragenus ∝ Gram-neg. bacillus many	Staph. albus many *Strept. (green)* ∞ *Strept. (grey)* few Tetragenus many
	July 19—*æt.* 6 hrs. (has not nursed)	July 20—*æt.* 31 hours	July 22—*æt.* 3 days	July 29—*æt.* 10 days
Case IX—Ce...	No growth	Staph. albus 50 *Strept. (green)* ∞ Lactis aërogenes 4	*Strept. (green)* ∞ Tetragenus many	Staph. albus few *Strept. (green)* ∞ Staph. aureus few

* ∝ = innumerable.

[1] The numbers indicate number of colonies.

TABLE I—CONTINUED

	July 22—*æt.* 20 hrs. (has just nursed)	July 23—*æt.* 2 days	July 29—*æt.* 8 days	
Case X—H....	*Strept.* (*green*) ∞ Tetragenus 50 Gram-neg. cocci 50 Diphtheroid few	*Strept.* (*green*) ∞ Tetragenus many Staph. albus 5 Staph. aureus 1	*Strept.* (*green*) ∞ Tetragenus few *Strept.* (*grey*) few Staph. albus many	
	July 23—*æt.* 1½ hrs. (has not nursed)		Aug 2—*æt.* 10 days	
Case XI—Hi...	No growth		Staph. albus sev. hundred Tetragenus few *Strept.* (*grey*) many *Strept.* (*green*) few	
	July 14—*æt.* 1 hr. (has not nursed)	July 15—*æt.* 1 day	July 19—*æt.* 5 days	July 23—*æt.* 9 days
Case XII—Ch..	No growth	Staph. aureus 1 Tetragenus sev. hundred *Strept.* (*grey*) many	Staph. aureus 6 Tetragenus many *Strept.* (*grey*) many Staph. albus ∞ Diphtheroids few	*Strept.* (*grey*) ∞ Staph. albus ∞ Diphtheroids few *Strept.* (*green*) many
	Aug. 20—*æt.* 23 hrs. (has nursed)	Aug. 22—*æt.* 3 days	Aug. 28—*æt.* 9 days	
Case XIII—K..	Staph. albus 10 Gram-neg. cocci 20 Gram-neg bacillvs 50 *Strept.* (*green*) ∞	Staph. albus 20 Gram-neg cocci ∞ *Strept.* (*green*) ∞ Diphtheroids few	Staph. albus few *Strept.* (*green*) ∞ Tetragenus ∞	
	Aug. 23—*æt.* 1 hr. (has not nursed)	Aug. 24—*æt.* 1 day	Aug. 26—*æt.* 3 days	Aug. 28—*æt.* 5 days
Case XIV—W..	No growth	Staph. albus few Gram-neg. cocci many *Strept.* (*green*) many	Gram-neg. cocci many *Strept.* (*green*) ∞ *Strept.* (*grey*) ∞ Tetragenus ∞ Staph. aureus 10	Staph. albus few Gram-neg. cocci few *Strept.* (*green*) ∞ *Strept.* (*grey*) ∞ Tetragenus few
	Aug. 17—*æt.* 23 hrs. (culture while nursing)	Aug. 18—*æt.* 2 days	Aug. 20—*æt.* 4 days	Aug. 25—*æt.* 9 days
Case XV—N...	*Strept.* (*grey*) ∞ *Strept.* (*green*) ∞ Tetragenus ∞ B. lactis aërogenes 50	*Strept.* (*grey*) ∞ *Strept.* (*green*) few Tetragenus ∞	*Strept.* (*grey*) many *Strept.* (*green*) many Tetragenus ∞ Staph. albus 200	*Strept.* (*grey*) ∞ *Strept.* (*green*) ∞ Tetragenus 1 Staph. albus 50
	Aug. 14—*æt.* 23 hrs. (has nursed)	Aug. 22—*æt.* 3 days	Aug. 24—*æt.* 5 days	Aug. 29—*æt.* 9 days
Case XVI—A.C.	Staph. albus 10 Gram-neg. cocci few Tetragenus sev. hundred *Strept.* (*grey*) ∞ *Strept.* (*green*) ∞	Staph. albus ∞ Tetragenus many *Strept.* (*green*) ∞ *Strept.* (*grey*) many Diphtheroids few	Staph. albus many Tetragenus ∞ *Strept.* (*green*) ∞ *Strept.* (*grey*) ∞ Staph. aureus 50	Staph. albus few Tetragenus ∞ *Strept.* (*green*) ∞ *Strept.* (*grey*) ∞ Staph. aureus few
	Aug. 15—*æt.* 3 hrs. (has not nursed)	Aug. 16—*æt.* 1 day	Aug. 18—*æt.* 3 days	Aug. 23—*æt.* 8 days
Case XVII—Ca.	Staph. albus 4 Diphtheroid 2	Tetragenus ∞ *Strept.* (*green*) ∞ *Strept.* (*grey*) ∞	Tetragenus ∞ *Strept.* (*green*) many *Strept.* (*grey*) ∞ Staph. aureus 6	Staph. albus 10 Tetragenus many *Strept.* (*green*) ∞ *Strept.* (*grey*) ∞ Staph. aureus ∞
	July 19—*æt.* 24 hrs. (has nursed)	July 22—æt. 4 days	Aug. 1—*æt.* 14 days	Aug. 3—*æt.* 16 days	Aug. 10—*æt.* 26 days
Case XVIII—Fr	Tetragenus 300 *Strept.* (*green*) ∞ Diphtheroids ∞ Beta hemol. strept. 100	*Strept.* (*green*) many Diphtheroids few Beta hemol. strept. 10 Staph. albus ∞ Gram-neg. coccus ∞	Staph. albus 300 Gram-neg. coccus ∞	Tetragenus many Staph. albus ∞	Tetragenus sev. hund. *Strept.* (*green*) ∞ *Strept.* (*grey*) ∞ Staph. albus 100

hemolytic, were encountered, the type often differing in successive cultures from the same infant. The organisms corresponded with the varieties found on the skin (see below). Their logical source is clearly the mother's skin and the milk, and this supposition is supported by the much lower incidence of white staphylococci in adults. There seemed to be no evidence of a real carrier state, but the presence of these bacteria indicates multiple transient infestations derived from nursing at four-hour intervals.

2. *Staphylococci (aurei).*—These organisms were found in a few cultures—in no case as constant inhabitants. Their significance was clearly that of transients derived from the mother's skin and milk.

3. *Micrococcus Tetragenus.*—Organisms of this group were found in a large percentage of the cultures but by no means constantly. Two main types were encountered (1) large uniformly Gram-positive forms in clumps and groups of four, and (2) smaller forms, many of which failed to retain the Gram stain. The colony formation also varied markedly. These organisms are common skin inhabitants, which pretty clearly explains their source.

4. *Diphtheroids.*—In marked contrast with what occurs in adults, diphtheroids were found only in occasional cultures and then in small numbers. Their significance was clearly that of transients, and their ubiquity on the skin surfaces and in the mouths of adults offers a ready explanation of their source. There was, however, no tendency to extensive or permanent growth on the mucous membranes of infants.

5. *Gram-negative cocci.*—These organisms are found practically constantly and in large numbers in the mouths of adults. In sharp contrast to this observation was their incidence in infants. We found them in only four cases of the series (II, VII, X, XIII).

6. *Streptococci.*—This group was of particular interest. As is seen in the table, streptococci appeared early, usually within 24 hours, and in nearly every case were constantly present in large numbers. Two main types were encountered, first, small green-producing colonies consisting usually of elongated cocci in long chains, which exhibited many variations in form and much variability to Gram staining, and secondly, small grey colonies of intensely Gram-positive forms in short chains. No obvious source for these organisms in the infants surroundings was found save the mouths of the attendant adults.

7. *Other Organisms.*—A variety of other organismsm were encountered in single instances—clearly transients of no significance—a Gram-negative bacillus (Cases VI, and VIII), *B. lactis aërogenes* (Cases IX and XV). In Case XVIII beta hemolytic streptococci were obtained in small numbers on the first two cultures. They were clearly transients and did not colonize or produce disease, but their source was obscure. Unfortunately, no examination of the mother's milk or breasts was made.

In summary, then, the infant's mouth, sterile at birth, rapidly becomes the site of profuse bacterial growth. The flora is relatively simple compared to that of adults consisting essentially of (1) a group of organisms constantly introduced during the process of nursing and corresponding pretty clearly with that of the skin of adults—Staphylococcus albus, M. tetragenus, Staphylococcus aureus, etc., (2) a small group of variable transients, and (3) non-hemolytic streptococci.

With a view to confirming the source of some of the above organisms a series of cultures was made from the skin and from the breast nipples of a group of adults associated with the infants. A swab dipped in sterile salt solution was rubbed over an area about one inch in diameter and plated on the same kinds of media used for the throat cultures. The results summarized in Tables II and III indicate the source of certain of the organisms found in the infants' mouths, such as albus, aureus, tetragenus, etc.

TABLE II

CULTURES FROM SKIN OF ARM OF ADULTS

M.—50 colonies Staph. albus (non-hemolytic).
4 colonies Staph. albus (hemolytic).
6 colonies M. tetragenus.
A few colonies of a coarse rod-like Gram-neg. bacillus.

E.—50 colonies Staph. albus.
1 colony Staph. aureus.
Many colonies Gram-neg. coccus.

C.—1 colony Staph. albus (non-hemolytic).
2 colonies Staph. albus. (hemolytic).
2 colonies Staph. aureus.
Many colonies spore-bearing Gram-neg. bacillus.
Many colonies M. tetragenus.

G.—Many colonies M. tetragenus.
A few colonies Gram-neg. cocci.
A few colonies Staph. albus.
2 colonies Staph. aureus.

S.—∞ colonies Staph. albus (hemolytic).
A few colonies Staph. albus (non-hemolytic).
Many colonies M. tetragenus.
A few Gram-pos. diphtheroids.

J.—Many colonies Staph. albus.
A few M. tetragenus.

D.—A few colonies Staph. albus.
A few colonies M. tetragenus.
A few colonies Gram-pos. diphtheroids.
A few colonies Gram-neg. diphtheroids.

A.—1 colony Staph. albus.

E.—12 colonies Staph. albus.
1 colony coarse Gram-neg. bacillus.

C.—12 colonies Staph. albus.

D.—Spreaders.

TABLE III

CULTURES FROM NIPPLES OF LACTATING WOMEN

Case 1—∞ colonies Staphylococci (several kinds).
Many colonies M. tetragenus.
Many colonies Diphtheroids.
A few colonies spore-bearing bacilli.

Case 2—∞ colonies Staphylococci (white).
Many colonies Gram-positive spore-bearer.
Many colonies M. tetragenus.
A few colonies spreaders.

Case 3—Many colonies M. tetragenus.
Many colonies Staph. albus.
Many colonies Gram-positive bacillus.

TABLE III—CONTINUED

Case 4—∞ colonies Staph. albus.
Many colonies M. tetragenus.
A few colonies Staph. aureus.
∞ colonies Gram-positive diphtheroids.
Case 5—A few colonies Staph. albus.
Many colonies Gram-negative coccus.
Many colonies Yeast.
Many colonies long chain—grey streptococcus.
Case 6—∞ colonies Staph. albus.
Many colonies M. tetragenus.
A few colonies Staph. aureus.
Many colonies Diphtheroids
Spreaders.

DISCUSSION

Above we have outlined the bacteriological facts elicited in the present study. A few words may now be devoted to the general questions raised at the beginning of the paper. It was hoped that further information might be obtained about the mucous membranes of the upper air passages as sites for bacterial growth and the nature of their relation to the organisms found. It may be recalled that in healthy adults we deal with an apparently habitual constant and completely adapted flora, with transients, and with foreign organisms associated with acute disease or chronic foci of infection. The question of another group of partly adapted organisms has been raised in another place[5] and evidence of their occurrence collected. In the present work it is of interest to note the absence of such organisms as influenza bacilli, pneumococci, and hemolytic streptococci which are relatively frequent in adults. Without direct contact observations no definite conclusions can be drawn, but the absence of these organisms raises the possibility of an inherent lack of complete adaptation to free growth in the throat, and suggests that special conditions are necessary for their colonization.

Of major importance, however, from the present point of view is the practically constant finding of non-hemolytic streptococci in large numbers beginning within a few hours after birth. One seems forced to conclude that an inherent adaptation to free growth on the mucous membranes of the upper air passages exists in the case of this group of bacteria. We state the matter in this way at the present time, for as yet no exact information is available as to actual chemical or biological factors which allow the colonization of this group rather than that of hemolytic streptococci or a host of other organisms. These observations do, however, seem to give a hint that subtle biological adaptations are of importance in explaining the presence of bacteria under certain conditions, rather than the cruder and more specific chemical facts of bacterial growth demonstrable in the test-tube.

BIBLIOGRAPHY

1. Bloomfield, A. L.: Bull. Johns Hopkins Hosp., 1920, XXXI, 118.
2. *Idem:* Bull. Johns Hopkins Hosp., 1921, XXXII, 1.
3. Brailovsky-Lounkevitch: Ann. de l'Institut Pasteur, 1915, XXIX, 379.
4. Bloomfield, A. L.: Journal Am. Med. Assn., 1921, LXXVII, 187.
5. *Idem:* Bull. Johns Hopkins Hosp., 1921, XXXII, 387.

DERMOID CYSTS OF THE OVARY

A REPORT OF FOUR CASES

By KARL H. MARTZLOFF

(From the Department of Gynecology of The Johns Hopkins Hospital and University)

1. A small dermoid cyst accidentally discovered by needling an enlarged ovary.

2. A large dermoid of the left ovary; a small dermoid cyst of the right ovary.

3. A dermoid cyst in the wall of a large multilocular ovarian cystadenoma.

4. A spinal-cell carcinoma developing in a dermoid cyst of the ovary.

These four cases of dermoid cyst of the ovary are presented not because such growths are rare, but because the pathological specimens came to our laboratory in rapid sequence and each case presented something of interest either clinically or pathologically. The case histories and pathological findings in brief are as follows:

CASE 1.—G. G., a white female, unmarried, 24 years old, was operated on by Dr. Cullen at the Church Home and Infirmary, November 15, 1920. The patient had had several attacks of pain localized in the right iliac and the inferior portion of the right lumbar quadrants. Some of these attacks had been associated with nausea, vomiting and a chill. The history was otherwise irrelevant. On account of the iliac pain the patient herself asked for a careful examination of the ovary.

The physical examination was essentially negative except for definite abdominal tenderness and muscle spasm on deep palpation over McBurney's point. A pelvic examination was not made.

At *operation* the appendix was found to be involved in a well-marked chronic inflammatory process. It was removed. The right tube and ovary were next brought to view through the (gridiron) incision. The tube appeared to be normal. The ovary, however, was about half as large again as normal, and presented several large follicular cysts. Three of these were punctured with a straight intestinal needle, and all yielded a clear, colorless fluid. The ovary, however, being still somewhat too large, the needle was passed deeply into its median half where no definite cyst was apparent, and immediately there escaped a very small drop of an oily fluid, which against the white surface of the ovary and on account of the good illumination appeared as a small, shimmering globule. The diagnosis being evident, an elliptical incision was made over the surface of the ovary and a dermoid cyst about 3 cm. in diameter was at once encountered. This was shelled out intact, about two-thirds of the ovary being left. The left ovary was normal.

Pathological Examination (Gyn. Path. No. 26372).—The specimen consists of a small tumor mass measuring 3.5 x 3 x 3 cm. (Fig. 1).

About one-half of this mass (marked "dermoid cyst") has a regular, pale gray surface with a few fine shreds of pale gray tissue attached. On palpation this portion is of semi-fluid consistence and possibly is slightly fluctuant. The other part, which represents the portion of the ovary included in the elliptical incision, appears elevated, pale red, smooth, glistening and translucent. On section a thin-walled cyst is seen filled with a gray, granular, greasy material which is soft and contains a few strands of hair. In one portion of the wall is an elevated, thickened area from which a tuft of hair projects. The cyst wall is as thin as tissue paper except over the portion where some ovarian tissue is attached; here it is 3 mm. thick and has several smooth-walled, cystic areas in its substance.

Microscopic examination shows the picture of an ordinary simple dermoid cyst lined with stratified epithelium several layers thick. In the wall of the cyst are numerous hair follicles and sebaceous glands. In its cavity are pink-staining detritus and some strands of hair. The cystic areas to one side are thin-walled structures lined with a single layer of flat or low cuboidal epithelium. These are enlarged Graafian follicles.

Comment.—The point of particular interest in this case is the discovery of a dermoid cyst embedded in the substance of an ovary so as to be entirely surrounded by ovarian tissue. Careful scrutiny of the fluid obtained by paracentesis led to the discovery of a dermoid cyst which would otherwise have been overlooked, and the patient would very probably, at some later date, have been compelled to submit to another abdominal operation. The value of paracentesis ovarii as a diagnostic procedure is well brought out in this case and can equally well be applied to other selected cases of small ovarian enlargement when it is desirable to be particularly conservative in preserving ovarian tissue and when the spilling of some of the cyst contents will not lead to peritoneal implantations as sometimes happens in ovarian papillary cystadenomata.

CASE 2.—M. M. (Gyn. No. 26756), a white, married woman, 2-para, 39 years old, was admitted to The Johns Hopkins Hospital April 6, 1921, complaining of pain in the lower part of the abdomen. There was nothing of importance in the family or personal history. The menstrual history was normal.

Present Illness.—For about a year the patient had complained of a dull pain in the left iliac quadrant and gradually had become conscious of a mass in this situation which seemed to be enlarging, so that finally it gave rise to a sense of fullness whenever she sat down.

The *physical examination* was essentially negative except for the presence of a firm, rounded, smooth mass which was movable and apparently about 15 cm. in diameter. This mass was situated in the left iliac fossa and extended upward to a point mid-way between the umbilicus and the symphysis pubis in a position in front of and to the side of the uterus, which appeared to be essentially normal. The right ovary was in its usual position and seemed to be about twice the normal size.

At *operation*, April 9, 1921, the left ovary was represented by a large tumor mass lying in the left iliac fossa and twisted on its pedicle through an arc of 90° (Fig. 2). The left tube and ovary were removed in the usual manner. The right ovary also contained a yellowish cyst, through the wall of which some hair could be seen. This cyst was resected, leaving *in situ* about what would correspond to one-third of a normal ovary. The usual prophylactic appendectomy was performed and the uterus was left in good position by a modified Coffey suspension.

Pathological Examination (Gyn. Path. No. 26756).—The resected portion of the right ovary measures 4.5 x 3 x 2 cm. It is smooth, pale gray and glistening except for one area where the surface has some small vesicle-like areas which are yellow, glistening and translucent. The tumor is doughy in consistence. On section (Fig. 2; insert) a cystic structure is seen filled with a sebaceous material in which there is some hair. The hair grows in a tuft from the inner aspect of the roughened yellow area noted on the external surface. The lateral portion of the mass, where it has come in contact with the normal ovarian substance, has several small, yellow, cystic areas.

The tumor mass on the left measures 12 x 10 x 9 cm. and has attached to it a normal Fallopian tube. The tumor is smooth, glistening, reddish, and a fine tracery of blood vessels is seen over its surface. It is doughy in consistence and on section presents the appearance of an ordinary dermoid cyst with very little hair.

Sections of the tumor removed from the right ovary show a thin wall, the inner aspect of which is lined with a stratified squamous epithelium, without papillæ, beneath which are numerous hair follicles. The yellow cystic areas seen in the gross are small cavities lined with stratified epithelium and here one also sees numerous multinuclear giant cells scattered in the stroma forming the cyst wall.*

Sections from the large cyst on the left show a similar inner epidermal lining, without papillæ but with an occasional hair follicle and sebaceous gland. Numerous epidermal inclusions are seen, some of these having the appearance of undifferentiated sweat glands.

Comment.—This patient passed through an uncomplicated convalescence and when last heard of had been menstruating normally at 26-day intervals. The case affords a good illustration of the feasibility of conserving the ovarian function when some normal tissue is present, thereby avoiding the danger and inconvenience of a premature operative menopause. The dermoid cysts are interesting in that they replaced about five-sixths of what should have been normal ovarian stroma; nevertheless, the patient has had and is still having her normal catamenia.

CASE 3.—L. T., a white woman, 35 years old, married, 3-para, was admitted to the Church Home and Infirmary March 27, 1921, complaining of an abdominal tumor and indigestion. The family and personal history have no bearing upon the case; the menstrual history had been normal.

Present Illness.—One year before admission the patient first noticed that she had an abdominal tumor which had gradually become larger.

The *physical examination* was essentially negative except for the abdominal findings. A large, symmetrical, rounded, and freely movable tumor mass was felt in the hypogastrium extending from the pelvis up to the umbilicus. This tumor could not be differentiated from the uterus on pelvic examination and we thought we were dealing with a freely movable myomatous uterus.

Operation.—The patient was operated on by Dr. Cullen on March 28, 1921. A small quantity of free straw-colored fluid was found in the pelvis. The right ovary was represented by a large ovarian cyst, which with its Fallopian tube was removed. Convalescence was uneventful and the patient is now well and free of all symptoms.

Pathological Examination (Gyn. Path. No. 26733).—The specimen consists of a large blue-domed mass to which is attached a Fallopian tube. The latter measures 10 x 1 cm. It is flattened out and stretched over the tumor mass. Its surface is covered by a smooth and glistening serosa, its lumen is patent and its fimbriæ are delicate. A small appendix vesiculosa is present.

The tumor mass measures 20 x 17 x 10 cm. Its surface has a bluish sheen, is smooth, glistening, and slightly irregular in outline. Palpation elicits definite fluctuation. On section a large multilocular cystic structure (Fig. 3) is seen. It was filled with a thick, tenacious,

* Dr. Cullen has frequently drawn attention to these giant cells and he feels that they are the precursors of the squamous epithelium. He goes further and states that "wherever an alveolar structure is noted in an ovary and where these alveolar spaces are more or less lined with giant cells, one can be absolutely certain that a dermoid cyst exists in that ovary."

glistening, glairy, translucent, mucinous material. One area in the cyst opposite the tube has a rather honey-combed, bubble-like appearance and here the contents are particularly viscous. On the inferior portion of the posterior wall of the cyst is seen an encapsulated mass different from the remainder of the cyst and measuring on its cut surface 1.7 x 1.5 cm. (Fig. 3; insert). It is easily recognized as a dermoid cyst containing some yellowish-gray, greasy material and a few strands of hair which do not appear to grow as a tuft from any one situation.

Sections from various portions of the cyst wall show a scanty stroma with numerous capillaries and occasional areas of round and polymorphonuclear cell infiltration. The inner aspect of the cyst wall is lined with a single layer of columnar epithelium which only in a few places is thrown up into a low fold. The individual cells are goblet-shaped and have a pink-staining cytoplasm with a pale central zone and a well-defined cell outline. The nuclei are at the base of the cells, are oval or round and in some cells are crescentic in shape. The cells rest on a poorly defined membrana propria. The smaller cystic areas mentioned in the gross description contain a moderate quantity of a homogenous, pink-staining material in which are large vacuoles. In short, it is a picture of a typical multilocular cystadenoma. Sections of the dermoid cyst taken through its wall where it borders the cavity of the multilocular ovarian cyst (Fig. 4) show the dermoid lined with several layers of cuboidal epithelium. In its wall are hair follicles as well as sweat and sebaceous glands. In the cavity of the dermoid is some detritus in which can be identified some strands of hair. The dermoid is separated from the cavity of the adjoining cyst by a narrow strand of pink-staining fibrous stroma which in turn is lined with a single layer of columnar epithelium similar to and continuous with the previously described epithelium lining the remainder of the multilocular cyst. No recognizable ovarian stroma is seen.

Comment.—This is the first time in the history of this hospital, as far as the records of the gynecological and pathological departments show, that a dermoid cyst has been seen in association with, and included in, the wall of a multilocular pseudomucinous cystadenoma of the ovary. Although pseudomucinous cysts of the ovary are not particularly rare and dermoid dysts of the ovary are even less uncommon, nevertheless, this particular pathological association is very unusual and the literature on it is quite meagre.

Case 4.—E. R., a white woman, married, 37 years old, 3-para, was admitted to the Church Home and Infirmary complaining of a "lump in her stomach" and was operated on by Dr. Cullen, March 1, 1921. There is nothing of importance in the family or personal history. Her menstrual history is apparently normal.

Symptoms of the *present illness* were first noted in December, 1920, when she began to have discomfort in the hypogastrium, and a sense of pressure, most noticeable near the rectum, which was aggravated by exercise and by the sitting posture. Lying down gave marked relief. The patient had felt a tumor mass in her abdomen about two months before entering the hospital and she was certain that the tumor had definitely, though slowly, increased in size.

The *physical examination* was essentially negative except for the abdominal findings. The liver edge was felt just below the costal margin, being sharp, of about normal consistence and not tender. The lower half of the abdomen was quite tender, especially in the left iliac quadrant. Here a firm, tender, mass was felt extending from the left iliac fossa upwards to within 3 cm. of the level of the umbilicus. This same mass could be felt behind the cervix and was only moderately movable on bi-manual manipulation.

At *operation* a quantity of oily fluid containing white flakes and grumous-like material was found free in the peritoneal cavity. The site of the left ovary was occupied by a ruptured cyst which extended out into the left side of the pelvis and lay upon the rectum behind, its anterior and medial surfaces being adherent to the posterior aspect of the uterus. This tumor mass with its attached Fallopian tube was removed as completely as possible, but a portion was left attached to the left side of the cervix. The peritoneal cavity was drained with two pelvic and two abdominal cigarette drains.

The patient had an intermittent pyrexia up to 101° F. for two days after the operation. At times she was jaundiced, bile was found in her urine, and she had constant rectal pain up to the time of her discharge from the hospital, March 27, 1921. She failed rapidly and died at her home June 21, 1921.

Pathological Examination (Gyn. Path. No. 26643).—The specimen consists of a Fallopian tube attached to a tumor mass (Fig. 5). The Fallopian tube, 7 x 0.5 cm., is pale gray, smooth, and glistening; its fimbriæ are delicate. The tumor mass measures 10 x 8 x 7 cm. It occupies the position of an ovary in relation to the tube to which it is attached by a meso-ovarium which has a normal appearance. Its outline is rather irregular and it has several distinct nodular areas. The portion of the tumor adjoining the proximal part of the tube is pale gray, smooth, glistening, and fluctuant, while the part inferior to the distal segment of the tube is pale gray, and firm, with opaque yellow nodular areas. The most dependent of these nodular areas, *a*, has a roughened surface which shows some loss of substance, just at the point where the tumor had been adherent to and blended with the cervix. On section the tumor is seen to be a unilocular cyst with a dirty brown liquid content in which are seen small, flattened yellow masses and large quantities of hair. Its walls measure from 1.5 mm. to 3.5 cm. in thickness; they are smooth and somewhat irregular, the irregularities corresponding to the nodular areas seen externally. At its thickest part, *a*, the external surface is rough and shows some loss of substance, while its internal aspect has several tufts of hair arising from it. The cut surfaces of this area are yellow, opaque, and granular, with pale gray, glistening and translucent columnar areas, which appear to be invaginations or ingrowths from the external surface. The other areas of nodular thickening show quite smooth surfaces both externally and on section.

In *sections* taken through various portions of *a* the cyst is lined with a stratified epithelium, eight to ten cells thick. These cells are round and oval, their nuclei take a fairly deep blue color with the hematoxylin and eosin stain and most of them have well-defined nucleoli. Each nucleus is surrounded by a small quantity of eosin-staining cytoplasm. The cells are irregular in size, shape, and staining reaction, large mononuclear forms and mitotic figures being common. There is no papillary arrangement of the epithelium, no stratum germinativum as such is observed, nor are any hair follicles, sebaceous or sweat glands seen. As one follows the epithelium along from the thinner portion over into the thicker part of the cyst wall, a marked metaplasia is noted and the cells invade the cyst wall in long strands and solid alveoli (Fig. 6). Much central necrosis is present in the alveoli and many bizarre degeneration forms are seen. Numerous epithelial pearls, giant cells and mitotic figures also occur. The tumor in places occupies the entire cyst wall and penetrates it at one point over a fairly broad area. The predominant type of tumor cell is round or polyhedral, with a nucleus which has a finely granular chromatin distribution with a well-defined, dark-blue-staining nucleolus and is surrounded by a moderate quantity of cytoplasm. This cytoplasm takes a faint eosin stain or no stain at all and is surrounded by a well-defined pink cell membrane.

Sections through *b* (Fig. 5) show a picture similar to that seen in the sections taken from *a*, with the exception that no epithelial pearls are observed and the neoplastic process, while involving the entire thickness of *b*, does not penetrate the serosa. The epithelium lining the inner surface of the cyst about the periphery of this nodule (Fig. 7) is stratified, three to four cells thick; it shows no evidence of malignant metaplasia, being identically the same as the epithelium from other non-malignant portions of the cyst wall.

Sections through *a* (Fig. 5) show a picture similar to those from *b*, there being no microscopic continuity between the two neoplastic processes.

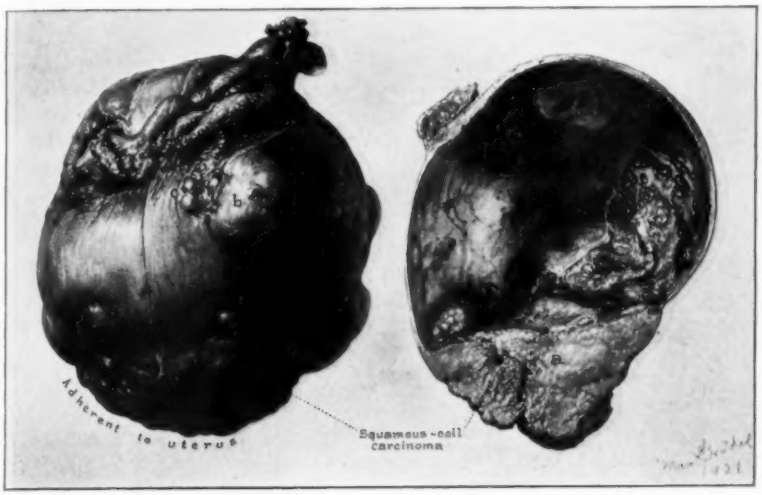


FIG. 5.—Gyn. Path. No. 26643. Case 4. Spinal cell carcinoma in a dermoid cyst of the ovary.

FIG. 6.—Case 4 (Gyn. Path. No. 26643). Section from Fig. 5 (a) showing spinal cell carcinoma with epithelial pearl at (a).

FIG. 7.—Case 4 (Gyn. Path. No. 26643). Section from nodule (b). (Fig. 5.) At the upper margin is the epidermal lining of the cyst, being here only a few cells thick and showing no evidence of malignant change. Two low power fields to the right of this area the epithelium assumes the character of that seen in Fig. 8 and invades. At the most inferior part of the photomicrograph is seen a small clump of cancer cells. This picture is taken from the periphery of (b) to show the benign appearance of the epithelium which completely surrounds these carcinomatous nodules.

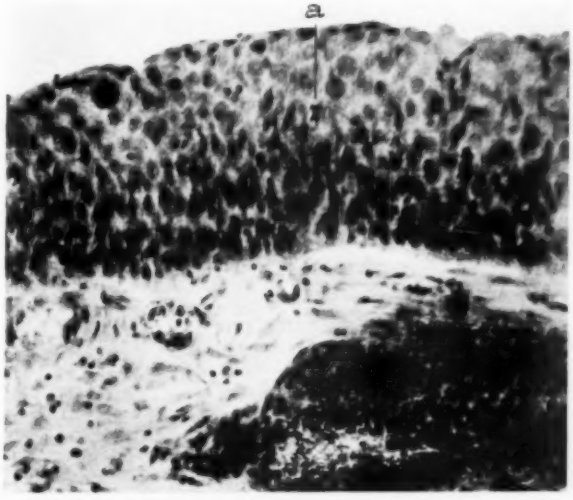


FIG. 8.—Case 4 (Gyn. Path. No. 26643). From the cyst wall adjacent to the meso-ovarium showing the thickness of the epithelium without invasion. These cells under high power show numerous mitotic figures and marked irregularity in size, shape, and staining reaction. Mitotic figure at (a).

FIG. 1.—Gyn. Path. No. 26372.

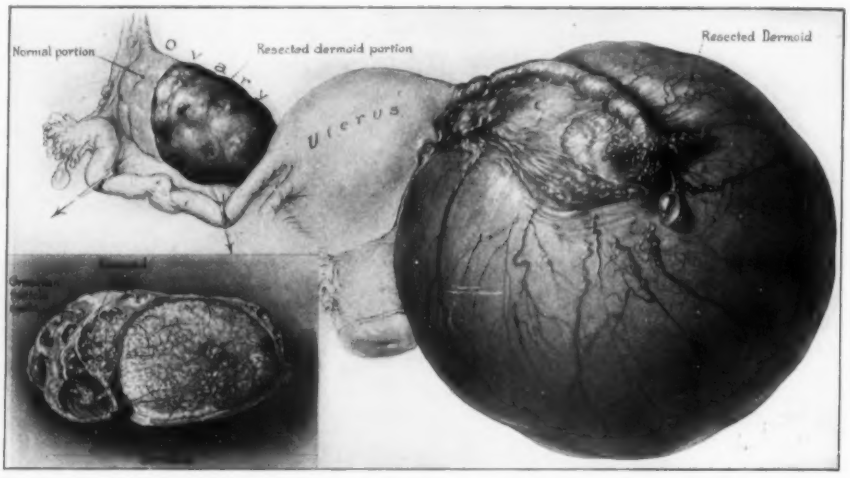


FIG. 2.—Gyn. Path. No. 26756. Case 2, showing the dermoid with its twisted pedicle on the left and the small quantity of normal ovarian tissue left on the right side after the resection.

FIG. 3.—Gyn. Path. No. 26733. Case 3. a multilocular pseudomucinous cystadenoma of the ovary containing a dermoid cyst.

FIG. 4.—Case 3 (Gyn. Path. No. 26733). From the dermoid cyst where it adjoins the cystadenoma. The columnar epithelium lining the cystadenoma is seen at the superior margin of the picture and the wall of the adjacent dermoid at the inferior margin.

The sections of the Fallopian tube and the meso-ovarium present nothing noteworthy. However, the adjacent wall of the cyst is lined with stratified epithelium, eight to twenty-five cells thick, which do not invade but are irregular in size, shape and staining reaction and show frequent mitotic figures (Fig. 8).

Comment.—It is interesting to note that while sections through *a* (Fig. 5) show many epithelial pearls, they are not seen in any of the others. The latter, however, show more well-defined cells and much less evidence of degeneration than at *a*. The carcinomatous change in various isolated portions of the cyst with intervening areas of non-malignant epidermal cells is striking and raises the question whether these small malignant nodules represent lymphatic metastases or whether they indicate separate foci of independent malignant change. The latter does not seem at all improbable when one considers the apparent malignant metaplasia without invasion noted in the epidermal cells (Fig. 8) lining the cyst in the portion adjacent to the meso-ovarium.

A simple dermoid cyst of the ovary, without evidence of a more complex teratomatous structure, undergoing malignant change, is in our experience very rare. Out of a total of some 200 patients who have had dermoid cysts in one or both ovaries (confirmed by examination of microsections) we have had only one other authentic case of carcinoma developing in an ovarian dermoid cyst. This occurred in 1899 in a white woman, 46 years old, who was lost track of. She was operated on, her convalescence proved unsatisfactory and she was not expected to live more than a few months after she left the hospital. It is reasonable to assume that she died as the result of the carcinoma. Sections showed a well-defined spinal cell carcinoma occurring in a dermoid cyst. The incidence of carcinomatous change occurring in a dermoid cyst of the ovary in this clinic is one per cent and our mortality from this disease is, we feel safe in saying, one hundred per cent.

I wish to express my indebtedness to Mr. Max Brödel and his pupil, Miss A. K. Lovett, for their excellent illustrations.

ADDENDUM

The value of puncture of the ovary as a practical diagnostic procedure was again demonstrated by Dr. Cullen in January, 1922, in the case of a young woman, C. H. I., No. 27512, whose history, operative findings, and treatment are almost a replica of Case 1 in this article.

TITLES OF PAPERS APPEARING DURING THE YEAR 1921, ELSEWHERE THAN IN THE BULLETIN, BY THE PRESENT AND FORMER MEMBERS OF THE JOHNS HOPKINS HOSPITAL AND MEDICAL SCHOOL STAFF

PREPARED IN THE LIBRARY

ATCHLEY, D. W., PALMER, W. W., and LOEB, R. F.
Studies on the regulation of osmotic pressure. I. The effect of increasing concentrations of gelatin on the conductivity of sodium chloride solution.—*J. Gen. Physiol.*, Balt., 1921, iii, 801-806.

AUER, J., and WITHERBEE, W. D.
Studies on decreasing the reaction of normal skin to destructive doses of X-rays by pharmacological means and on the mechanism involved.—*J. Exper. M.*, Balt., 1921, xxxiii, 791-813.

BAER, W. S.
Past, present and future of orthopedic surgery.—*South. M. J.*, Birm., Ala., 1921, xiv, 42-48.

BAER, W. S., BRACKETT, E. G., and RUGH, J. T.
Report of the Commission appointed to investigate the results of ankylosing operations of the spine.—*J. Orthop. Surg.*, Bost., 1921, iii, 507-514.

BAETJER, F. H., and WATERS, C. A.
Injuries and diseases of the bones and joints: their differential diagnosis by means of the roentgen rays.—N. Y., 1921, P. B. Hoeber. 349 p., 4°.

BAIRD, J. H.
The examination of the eye in neuro-surgical patients.—*Virginia M. Month.*, Richmond, 1920-21, xlvii, 532-536.

BARDEEN, C. R.
The relation of ossification to physiological development.—*J. Radiol.*, Omaha, Neb., 1921, ii, 1-8.
The von Pirquet standard of normal body weight as compared with other standards (Correspondence).—*J. Am. M. Ass.*, Chicago, 1921, lxxvii, 1988-1990.

BARKER, L. F.
Multiglandular syndromes. Survey of literature from Sept. 1, 1920, to March 1, 1921.—*In:* Nelson Loose-Leaf Med., Lond. & N. Y., 1921, iii, 238-239.
The importance of psychiatry in general medical practice.—*In:* A Psychiatric Milestone. Bloomingdale Hospital, 1821-1921. N. Y., 1921, 55-75. [Privately printed.]
Diagnostic criteria in epidemic encephalitis and encephalomyelitis.—*Arch. Neurol. & Psychiat.*, Chicago, 1921, vi, 173-196.
The value of drugs in internal medicine.—*J. Am. M. Ass.*, Chicago, 1921, lxxvii, 1151-1155.
The classical endocrine syndromes.—*N. York M. J.*, [*etc.*], 1921, cxiii, 353-363.
Neutrophilic myelocytes in the cerebro-spinal fluid of a patient suffering from myeloid leukemia and their significance for the diagnosis of myeloleukemic infiltration of the leptomeninges.—*South M. J.*, Birmingham, Ala., 1921, xiv, 437-442.
On the care of patients manifesting high blood pressure.—*Virginia M. Month.*, Richmond, 1921, n. s., xlviii, 1-7. *Also: South. M. & S.*, Charlotte, N. C., lxxxiii, 134-141.
Group diagnosis and group therapy.—*Illinois M. J.*, 1921, xxxix, 1-9. *Also: J. Iowa State M. Soc.*, 1921, xi, 113-120.

BAUMGARTEN, W., FISCHEL, W., and SOPER, H. W.
Hospital diets.—*J. Missouri M. Ass.*, St. Louis, 1921, xviii, 263.

BAYNE-JONES, S., and WILSON, D. W.
Specific immunological reactions of Bence-Jones proteins.—*Proc. Soc. Exper. Biol. & Med.*, N. Y., 1920-1921, xviii, 220-222.

BEALL, F. C.
The diagnosis of cancer of the colon.—*Texas State J. M.*, Fort Worth, 1921-22, xvii, 343-348.

BEALL, F. C., and JAGODA, S.
Injection of the bile ducts with barium.—*J. Am. M. Ass.*, Chicago, 1921, lxxvi, 1483-1484.

BEALL, K. H.
Epidemic encephalomeningomyeloneuritis ("Sleeping sickness").—*Texas State J. M.*, Fort Worth, 1921-22, xvii, 157-161.

BERNHEIM, B. M.
Whole blood transfusion and citrated blood transfusion; possible differentiation of cases.—*J. Am. M. Ass.*, Chicago, 1921, lxxvii, 275-279.

BERRY, J. M.
Further observations on the presence of roentgenological shadows associated with bursitis.—*Albany M. Ann.*, 1921, xlii, 54-59.
The differential diagnosis between tuberculosis of the hip and osteochondritis deformans juvenilis (Perthes) or osteochondral trophopathy of the hipjoint (Legg).—*Albany M. Ann.*, 1921, xlii, 90-93.
Perthes' disease.—*Albany M. Ann.*, 1921, xlii, 94-99.
An unusual exostosis of the tibia.—*Albany M. Ann.*, 1921, xlii, 130-131.
Reports from the Roentgen-ray Department of the Albany Hospital.—*Albany M. Ann.*, 1921, xlii, 347-355.

BIDGOOD, C. Y.
A study of methods of procedure in resection of the œsophagus.—*Ann. Surg.*, Phila., 1921, lxxiv, 546-556.

BLACKFAN, K. D.
Biologic therapy: III. The use of antimeningococcus serum in the treatment of epidemic meningitis.—*J. Am. M. Ass.*, Chicago, 1921, lxxvi, 36-37.

BLACKFAN, K. D., and LITTLE, K.
A clinical and radiographic study of the thymus in infants.—*Am. J. Dis. Child.*, Chicago, 1921, xxii, 459-470. *Also: Tr. Am. Pediat. Soc.*, 1921, xxxiii.

BLANTON, S.
The medical significance of the disorders of speech.—*J. Am. M. Ass.*, Chicago, 1921, lxxvii, 373-377.
Speech defects in school children.—*Ment. Hyg.*, N. Y., 1921, v, 820-827.

BLOCK, E. B.
The etiologic relation of worms to epilepsy.—*J. Med Ass. Georgia*, Atlanta, 1921, x, 309.

BLOODGOOD, J. C.
Cancer of the tongue a preventable disease (Correspondence).—*J. Am. M. Ass.*, Chicago, 1921, lxxvii, 220.
Cancer of the tongue: a preventable disease.—*J. Am. M. Ass.*, Chicago, 1921, lxxvii, 1382-87.
Early diagnosis of cancer.—*Wisconsin M. J.*, Milwaukee, 1921-22, xx, 235-236.
The pathology of chronic cystic mastitis of the female breast; with special consideration of the blue-domed cyst.—*Arch. Surg.*, Chicago, 1921, iii, 445-542.

BLOOMFIELD, A. L.
The serial quantitative method of culture in the study of respiratory disease.—*J. Am. M. Ass.*, Chicago, 1921, lxxvii, 187-192.
The mechanism of the bacillus carrier state with special reference to the Friedländer bacillus.—*Am. Rev. Tuberc.*, Balt., 1920-21, iv, 847-855.

BLUMER, G.
Gonococcus infection.—*In:* Oxford Med., 1921, v, 39-70.
Report of a case of extensive cavernous angioma of the head, face and neck, with attacks of fever and somnolence.—*Boston M. & S. J.*, 1921, lxxxv, 58-60.
Some remarks on "cases and observations by the Medical Society of New Haven County."—*Bull. Soc. Med. Hist.*, Chicago, 1921, ii, 205-218.
Group practice (Correspondence).—*J. Am. M. Ass.*, Chicago, 1921, lxxvii, 2081.
President's address. Connecticut State Medical Society.—*Proc. Connect. State Med. Soc.*, 1921, 69-77.

BOGGS, T. R., and PINCOFFS, M. C.
Diseases of the peritoneum.—*In:* Oxford Med., 1921, iii, 517-581.

BOWCOCK, H. M., and PAULLIN, J. E.
Recent improvements in dietetic treatment of diabetes mellitus.—*J. Med. Ass. Georgia*, Atlanta, 1921, x, 676.

BOYD, M. L.
Nephritis and general surgery.—*South. M. J.*, Birmingham, Ala., 1921, xiv, 368-371.

DU BRAY, E. S.
Saccular aneurysm of the descending thoracic aorta, with direct rupture into the lower lobe of the left lung and the left pleural cavity. The report of a case and remarks on rupture and hemoptysis in aortic aneurysm.—*Am. J. M. Sc.*, Phila., 1921, clxi, 407-418.

BROOKS, B., and ALLISON, N.
Bone atrophy: an experimental and clinical study of the changes in bone which result from non-use.—*Surg., Gynec. & Obst.*, Chicago, 1921, xxxiii, 250-260.

BROWN, N. W.
Determination of relative activity of the thyroid lobes.—*Endocrinology*, Glendale, Cal., 1921, v, 29-32.

BROWN, T. R.
Carcinoma and other tumors of the gastro-intestinal tract.—*In:* Nelson Loose-Leaf Med., Lond & N. Y., 1921, v, 295-299.
Tuberculosis of the gastro-intestinal tract.—*In:* Nelson Loose-Leaf Med., Lond. & N. Y., 1921, v, 301-308.
Ulcerations of the gastro-intestinal tract (Not including peptic ulcer).—*In:* Nelson Loose-Leaf Med., Lond. & N. Y., 1921, v, 309-310.
Rôle of diet in etiology and treatment of migraine and other types of headache.—*J. Am. M. Ass.*, Chicago, 1921, lxxvii, 1396-1400.
The absence of pancreatic secretions in sprue and the employment of pancreatic extract in the treatment of this disease.—*Am. J. M. Sc.*, Phila., 1921, clxi, 501-507.
A note on the administration of pancreatic extract in the treatment of sprue.—*J. Trop. M.* [etc.], Lond., 1921, xxiv, 90-92.

BUNTING, C. H.
Diseases of the lymph glands. Survey of literature from Sept. 1, 1920, to March 1, 1921.—*In:* Nelson Loose-Leaf Med., Lond. & N. Y., 1921, iii, 368.
The leukocytic picture in influenza.—*Am. J. M. Sc.*, Phila., 1921, clxii, 1-9.

BUNTING, C. H., and HUSTON, J.
Fate of the lymphocyte.—*J. Exper. M.*, Balt., 1921, xxxiii, 593-600.

BURROWS, M. T.
The causes of disease.—*J. Missouri M. Ass.*, St. Louis, 1921, xviii, 384-392.
The reserve energy of actively growing embryonic tissues.—*Proc. Soc. Exper. Biol. & Med.*, N. Y., 1920-21, xviii, 133-136.

BURWELL, C. S., and JONES, C. M.
The removal of bile and blood from the urine in performing the phenolsulphonephthalein test of renal function.—*J. Am. M. Ass.*, Chicago, 1921, lxxvii, 462-463.

BURWELL, C. S., and WHITE, P. D.
The clinical significance of changes in the form of the electrocardiogram.—*Med. Clin. N. Am.*, Phila., 1921, iv, 1839-1861.

BURWELL, C. S., WHITE, P. D., and MARVIN, H. M.
The action of quinidine sulphate in heart disease, to abolish the circus movement of auricular flutter and fibrillation.—*Boston M. & S. J.*, 1921, lxxxv, 647-650.

CAMAC, C. N. B.
The live wire mind (Editorial).—*J. Am. M. Ass.*, Chicago, 1921, lxxvii, 129-130.

CAMAC, C. N. B., *comp.*
Counsels and ideals, from the writings of William Osler. 2. ed. 1921, London. Oxford Press; Boston, Houghton, Mifflin & Co., 356 p. 8°.

CAMPBELL, C. M.
Personal factors in disease.—*In:* Nelson Loose-Leaf Med., Lond. & N. Y., 1921, vii, 145-153.
History of insanity during the past century, with special reference to the McLean Hospital.—*Boston M. & S. J.*, 1921, clxxxv, 538-544.
The use of drugs in neurology and psychiatry.—*J. Am. M. Ass.*, Chicago, 1921, lxxvii, 1228-1230.
Mental hygiene in industry.—*Ment. Hyg.*, N. Y., 1921, v, 468-478.
The education of the emotions.—*Proc. Head Mistresses Assoc.*, Bost., Mass., April, 1921.

CARTER, D. W., JR.
Irregularities of the heart beat.—*Dallas M. J.*, 1921, viii, 13.
The rôle of the pituitary body in the etiology and therapy of diabetes insipidus.—*Texas State J. M.*, Fort Worth, 1921, xvi, 491-495.

CASH, J. R.
On the development of the lymphatics of the stomach in the embryo pig.—*Contrib. Embryol.* No. 57, (Carnegie Inst.), Wash., 1921, xiii, 1-15.

CASH, J. R., and YOUNG, H. H.
A case of pseudohermaphrodismus masculinus showing hypospadias, greatly enlarged utricle, abdominal testis and absence of seminal vesicles.—*J. Urol.*, Balt., 1921, v, 405-430.

CAULK, J. R.
Factors which influence results and mortality rate in kidney surgery. Analytic study of two hundred and sixty-three operations.—*J. Am. M. Ass.*, Chicago, 1921, lxxvii, 843-848.
A new method of removing the median bar type of prostatic obstruction.—*J. Missouri M. Ass.*, St. Louis, 1921, xviii, 191.
Renal tuberculosis.—*J. Urol.*, Balt., 1921, vi, 97-113.
Presentation of a cautery punch for the removal of minor obstructions at the vesical neck, with new method of anesthesia.—*South. M. J.*, Birmingham, Ala., 1921, xiv, 816-819.

CHESNEY, A. M.
An immunologic study of bacillus influenzæ.—*J. Infect. Dis.*, Chicago, 1921, xxix, 132-140.

CHURCHMAN, J. W.
Sterilization of closed cavities by lavage and staining with gentian violet. Description of technic.—*J. Am. M. Ass.*, Chicago, 1921, lxxvii, 24-26.
Further studies on the behavior of bacteria toward gentian violet.—*J. Exper. M.*, Balt., 1921, xxxiii, 569-581.
The cause of the parallelism between the gram reaction and the gentian violet reaction.—*Proc. Soc. Exper. Biol & Med.*, N. Y., 1920-21, xviii, 17-18.
The isolation of gentian positive individuals from a suspension of a gentian negative organism (B. coli).—*Proc. Soc. Exper. Biol. & Med.*, N. Y., 1920-21, xviii, 19.
Relation of the gentian violet reaction to dilution of implanted suspension.—*Proc. Soc. Exper. Biol. & Med.*, N. Y., 1920-21, xviii, 20.
The effect of repeated re-inoculations of gentian violet agar with gentian positive organisms.—*Proc. Soc. Exper. Biol. & Med.*, N. Y., 1920-21, xviii, 20-21.
The selective action of gentian violet in relation to chemotherapy.—*Proc. Soc. Exper. Biol. & Med.*, N. Y., 1920-21, xviii, 21-22.

CHURCHMAN, J. W., and KAHN, M. C.
Communal activity of bacteria.—*J. Exper. M., Balt.*, 1921, xxxiii, 583-591. *Also: Proc. Soc. Exper. Biol. & Med.*, N. Y., 1920-21, xviii, 23-24.

CLARKE, T. W.
"Colic" in the nursing infant.—*N. York State J. M.*, N. Y., 1921, xxi, 138.

CLOUGH, M. C., and CLOUGH, P. W.
A study of the reactions following the transfusion of blood.—*South. M. J.*, Birmingham, Ala., 1921, xiv, 104-109.

COBB, S.
Some neurologic aspects of chorea.—*Med. Clin. N. Am.*, Phila., 1921, iv, 1863-1870.

COBB, S., and COLEMAN, C. C.
The course of recovery following trauma of the spinal cord.—*Arch. Surg.*, Chicago, 1921, iii, 132-139.

COBB, S., FORBES, A., and CATTELL, M.
An electrocardiogram and an electromyogram in an elephant.—*Am. J. Physiol.*, Balt., 1921, lv, 385-389.

COBB, S., and PARMENTER, D. C.
Headache.—*J. Indust. Hyg.*, N. Y. & Bost., 1921, iii, 173-178.

COLE, R.
Acute lobar pneumonia. (Survey of literature from Sept. 1, 1920, to March 1, 1921.) *In:* Nelson Loose-Leaf Med., Phila. & Lond., 1921, i, 276-277.
Antipneumococcus serum.—*J. Am. M. Ass.*, Chicago, 1921, lxxvi, 111-112.
Prevention and specific treatment of pneumonia.—*J. State Med.*, Lond., 1921, xxix, 58.

COLSTON, J. A. C.
The value of pyelography in the diagnosis of neoplasms of the kidney.—*J. Urol.*, Balt., 1921, v, 67-87.

CORNELL, W. B.
Group mental hygiene.—*Am. J. Insan.*, Balt., 1920-21, lxxvii, 335-342.
The organization of state institutions for feeble-minded in the United States.—*Canad. J. Ment. Hyg.*, Montreal, 1921, iii, 65-70.

CORNER, G. W.
Abnormalities of the mammalian embryo occurring before implantation.—*Contrib. Embryol.*, No. 60 (Carnegie Inst.), Wash., 1921, xiii, 61-66.
Cyclic changes in the ovaries and uterus of the sow, and their relation to the mechanism of implantation.—*Contrib. Embryol.*, No. 64 (Carnegie Inst.), Wash., 1921, xiii, 117-146.
A review of some recent work on the mammalian reproductive cycle.—*J. Mammalogy*, Balt., 1921, ii, 227-231.
A case of true lateral hermaphroditism in a pig with functional ovary.—*J. Urol.*, Balt., 1921, v, 481-485.
The ovarian cycle of swine.—*Science*, N. Y. & Lancaster, 1921, liii, 420-421.

COWDRY, E. V.
The Office of Imperial Physicians, Peking.—*J. Am. M. Ass.*, Chicago, 1921, lxxvii, 307-310.
The reticular material of developing blood cells.—*J. Exper. M.*, Balt., 1921, xxxiii, 1-12.

CRAWFORD, A. C., and GEORGE, J. M.
The testes and certain vaso-motor reactions of the penis.—*J. Urol.*, Balt., 1921, v, 89-118.

CULLEN, E. K.
Diverticulum of the first portion of the duodenum.—*Arch. Surg.*, Chicago, 1921, ii, 542-564.
Tuberculous ulcer of the anterior vaginal wall with resection of ulcer.—*Surg., Gynec., & Obst.*, Chicago, 1921, xxxiii, 76-78.

CULLEN, T. S.
Three cases of subperitoneal, pedunculated adenomyoma.—*Arch. Surg.*, Chicago, 1921, ii, 443-454.
The weak spot in American surgery.—*Surg., Gynec. & Obst.*, Chicago, 1921, xxxiii, 67-72.
Early squamous-cell carcinoma of the cervix, accidentally discovered when the body of the uterus was being curetted for hæmorrhage caused by hyperplasia of the endometrium and by a small submucous myoma.—*Surg., Gynec. & Obst.*, Chicago, 1921, xxxiii, 137-144.

CUSHING, H.
The personality of a hospital.—*Boston M. & S. J.*, 1921, clxxxv, 529-538.
Disorders of the pituitary gland; retrospective and prophetic.—*J. Am. M. Ass.*, Chicago, 1921, lxxvi, 1721-1726.
Further concerning the acoustic neuromas.—*Laryngoscope*, St. Louis, 1921, xxxi, 209-228.
The special field of neurological surgery after another interval.—*Illinois M. J.*, Oak Park, 1921, xxxix, 133-141; 185-195. *Also: Wisconsin M. J.*, Milwaukee, 1920-21, xix, 501-520. *Also: Ohio M. J.*, Columbus, 1921, xvii, 293-302; 373-380. *Also: J. Iowa State M. Soc.*, Clinton, 1921, xi, 337-342; 385-394; 426-430.

DANDY, W. E.
The treatment of brain tumors.—*J. Am. M. Ass.*, Chicago, 1921, lxxvii, 1853-1859.
The diagnosis and treatment of hydrocephalus due to occlusions of the foramina of Magendie and Luschka.—*Surg. Gynec. & Obst.*, Chicago, 1921, xxxii, 112-124.
An operation for the removal of pineal tumors.—*Surg., Gynec. & Obst.*, Chicago, 1921, xxxiii, 113-119.

DAVIDSON, E. C., and DIEUAIDE, F. R.
Terminal cardiac arrhythmias. Report of three cases.—*Arch. Int. Med.*, Chicago, 1921, xxviii, 663-677.

DAVIS, D. M., and SWARTZ, E. O.
Action of mercurochrome –220 on the gonococcus.—*J. Am. M. Ass.*, Chicago, 1921, lxxvi, 844-846.
The action on the gonococcus of various drugs commonly used in the prophylaxis and treatment of gonorrhea.—*J. Urol.*, Balt., 1921, v, 235-253.

DAVIS, E. G.
Urinary antisepsis: a study of antiseptic properties and the renal excretion of 204 aniline dyes.—*Am. J. M. Sc.*, Phila., 1921, clxi, 251-267.
The significance of hematuria. Report of 46 cases.—*J. Iowa State M. Soc.*, Clinton, 1921, xi, 315.
The Young-Stone operation for urethrorectal fistula. Report of three cases.—*Surg., Gynec. & Obst.*, Chicago, 1921, xxxii, 225-231.

DAVIS, E. G., and BECK, G. H.
Urinary antisepsis. The secretion of antiseptic urine by man following the oral administration of proflavine and acriflavine. Preliminary report.—*J. Urol.*, Balt., 1921, v, 215-233.

DAVISON, W. C.
Biologic therapy. xiii. Pertussis vaccine.—*J. Am. M. Ass.*, Chicago, 1921, lxxvi, 242-243.

DAVISON, W. C., and JOSEPHS, H. W.
The serotherapy of bacillary dysentery in children.—*J. Am. M. Ass.*, Chicago, 1921, lxxvii, 1863-1864.

DAVISON, W. C., and ROSENTHAL, L. V.
A bacteriological study of the fecal flora of infants and children (the lack of association of nutritional disorders with a so-called "putrefactive" intestinal flora).—*Am. J. Dis. Child.*, Chicago, 1921, xxii, 284-298.

DENZER, B. S.
The size of the infantile palate.—*Am. J. Dis. Child.*, Chicago, 1921, xxii, 471-476.

DENZER, B. S., and ANDERSON, A. F.
Absorption of fluid injected into the peritoneal cavity.—*Am. J. Dis. Child.*, Chicago, 1921, xxi, 565.

DICK, GLADYS H., and DICK, G. F.
Experimental inoculations in scarlet fever.—*J. Am. M. Ass.*, Chicago, 1921, lxxvii, 782-785.

DICKSON, E. C.
Botulismus.—*In:* Oxford Med., 1921, v, 231-257.
Pathology of botulism. (Correspondence.)—*J. Am. M. Ass., Chicago*, 1921, lxxvii, 483-484.

DICKSON, E. C., and SHEVKY, R.
Botulism; a study of the action of the toxin of *B. botulinus* upon the living tissues.—*Proc. Soc. Exper. Biol. & Med.*, N. Y., 1920-21, xviii, 313.

DIEUAIDE, F. R.
The determination and significance of the electrical axis of the human heart.—*Arch. Int. Med.*, Chicago, 1921, xxvii, 558-570.

DUNHAM, ETHEL C.
Peritonitis as a complication of scarlet fever.—*Am. J. Dis. Child.*, Chicago, 1921, xxii, 307-309.

DUNTON, W. R.
The psychosis of a famous portraitist.—*Maryland Psychiat. Q.*, Balt., 1921, x, 50-54.
The passing of the Henry B. Faville School.—*Maryland Psychiat. Q.*, Balt., 1921, x, 77-78.

EBAUGH, F. G., and HOSKINS, R. G.
A case of dystrophia adiposogenitalis.—*Endocrinology*, Glendale, Cal., 1921, v, 21-28.

ELMENDORF, D. F.
Vincent's angina.—*Mil. Surgeon*, Wash., 1921, xlix, 287-291.

EMERSON, C. P.
Clinical diagnosis. 5. ed. Phila. & Lond., 1921, J. B. Lippincott Co., 726 p. 8°.
The problem of the so-called primary anæmias from the internist's standpoint.—*Chicago M. Recorder*, 1921, xliii, 125-136.
Teaching of general medicine.—*J. Am. M. Ass.*, Chicago, 1921, lxxvi, 869.
The acute element in the chronic nephropathies.—*J. Am. M. Ass.*, Chicago, 1921, lxxvii, 745-749.

EMMONS, A. B., 2d.
Health in mercantile establishments. 111. Common sanitary defects in stores.—*J. Indust. Hyg.*, N. Y. & Bost., 1921, iii, 29-36.

EMMONS, A. B., 2d., and GOLDTHWAIT, J. E.
A work chair.—*J. Indust. Hyg.*, N. Y. & Bost, 1921, iii, 154-158.

ERLANGER, J.
Blood volume and its regulation.—*Physiol. Rev.*, Balt., 1921, i, 177-207.

ERLANGER, J., and WHITE, H. L.
The effect on the composition of the blood of maintaining an increased blood volume by the intravenous injection of a hypertonic solution of gum acacia and glucose in normal asphyxiated and shocked dogs.—*Am. J. Physiol.*, Balt., 1920-21, liv, 1-29.

ESTES, W. L., JR.
Early diagnosis of perforated gastric or duodenal ulcer.—*Penn. M. J.*, 1920-21, xxiv, 307-309.

EYSTER, J. A. E., and MEEK, W. J.
Reactions to hemorrhage.—*Am. J. Physiol.*, Balt., 1921, lvi, 1-15.
The origin and conduction of the heart beat.—*Physiol. Rev.*, Balt., 1921, i, 1-43.

FABYAN, M., TYZZER, E. E., and FOOT, N. C.
Further observations on "blackhead" in turkeys.—*J. Infect. Dis.*, Chicago, 1921, xxix, 268-286.

FELTON, L. D.
A colorimetric method for determining the hydrogen-ion concentration of small amounts of fluid.—*J. Biol. Chem.*, Balt., 1921, xlvi, 299-305.

FINNEY, J. M. T.
A personal appreciation of Sir William Osler.—*J. Am. M. Ass.*, Chicago, 1921, lxxvii, 2013-2019.
Acute intestinal obstruction.—*Surg., Gynec. & Obst.*, Chicago, 1921, xxxii, 402-408.

FINNEY, J. M. T., and FRIEDENWALD, J.
Pylorospasm in adults: its medical and surgical treatment.—*Am. J. M. Sc.*, Phila., 1921, clxii, 469-481.

FINNEY, W. P., JR.
Malignant tumors in the United States Army, 1917-1919.—*Mil. Surgeon*, Wash., D. C., 1921, xlviii, 672-676.

FLEURNOY, H.
Un asile d'aliénés au Japon. Communic. au Congrès des Médecins Aliénistes de France. Strasbourg, Août, 1921.

FLEXNER, S.
Biologic therapy. General considerations regarding serum and vaccine therapy.—*J. Am. M. Ass.*, Chicago, 1921, lxxvi, 33-34.
Biologic therapy. lv. Serum treatment of bacillary dysentery.—*J. Am. M. Ass.*, Chicago, 1921, lxxvi, 108-109.
Lethargic encephalitis. History, pathologic and clinical features, and epidemiology in brief.—*Stud. Rockefeller Inst. M. Research*, N. Y., 1921, xxxvi, 119-131.

FLEXNER, S., and AMOSS, H. L.
Experiments on the nasal route of infection in poliomyelitis.—*Stud. Rockefeller Inst. M. Research*, N. Y., 1921, xxxvi, 45-56.

FOLEY, F. E. B.
Clinical uses of salt solution in conditions of increased intracranial tension.—*Surg., Gynec. & Obst.*, Chicago, 1921, xxxiii, 126-136.

FOWLER, H. A.
Tuberculosis of the kidney complicated by impacted pelvic calculus.—*J. Urol.*, Balt., 1921, v, 345-351.

FRONTZ, W. A.
A clinical and pathological study of contracted bladder.—*J. Urol.*, Balt., 1921, v, 491-511.
The more common causes of chronic urinary obstruction in male children. Tr. South. Med. Assoc., 1921, xv. Abstr. *In: J. Am. M. Ass.*, Chicago, 1921, lxxvii, 1996.

GAENSLEN, F. J.
The diagnosis and treatment of chronic lesions of the hip-joint.—*Minnesota Med.*, Saint Paul, 1921, iv, 630-635.
Sling suspension method of exercise in infantile paralysis.—*Surg., Gynec. & Obst.*, Chicago, 1921, xxxii, 274-276.
Sacro-iliac joint arthrodesis by bone-splitting method.—*Wisconsin M. J.*, Milwaukee, 1921, xx, 20-22.

GAENSLEN, F. J., and SCHNEIDER, C. C.
Treatment of tuberculosis of the ankle in the adult.—*J. Am. M. Ass.*, Chicago, 1921, lxxvii, 1168-1171.

GAENSLEN, F. J., and THALHEIMER, W. M.
Congenital syphilitic epiphysitis in adolescence.—*J. Orthop. Surg.*, Bost., 1921, iii, 8-17.

GAITHER, E. H.
Interpretation of digestive symptomatology. Relative to change in symptoms and extrinsic factors.—*J. Am. M. Ass.*, Chicago, 1921, lxxvii, 1407-1410.
Chronic appendicitis.—*South. M. J.*, Birmingham, Ala., 1921, xiv, 190-199.

GERAGHTY, J. T.
Biologic therapy: II. Use of vaccines and serums in gonorrheal urethritis and its complications.—*J. Am. M. Ass.*, Chicago, 1921, lxxvi, 35.
Some general considerations regarding prostatectomy.—*South. M. J.*, Birmingham, Ala., 1921, xiv, 48-51.

GERAGHTY, J. T., SHORT, J. T., and SCHANZ, R. F.
Multiple renal calculi, unilateral and bilateral; some observations.—*J. Am. M. Ass.*, Chicago, 1921, lxxvii, 901-904.

GIFFIN, H. Z.
Present status of splenectomy as a therapeutic measure.—*Minnesota Med.*, St. Paul, 1921, iv, 132-138.

GIFFIN, H. Z., and SZLAPKA, T. L.
The treatment of pernicious anemia by splenectomy; second report.—*J. Am. M. Ass.*, Chicago, 1921, lxxvi, 290-295.

GILMAN, P. K.
Amebic abscess of liver.—*Calif. State J. M.*, San Fran., 1921, xix, 239.
Acute suppurative thyroiditis.—*Calif. State J. M.*, San Fran., 1921, xix, 294.
Branchial cysts and fistulas.—*J. Am. M. Ass.*, Chicago, 1921, lxxvii, 26-28.
Cysts and fistulæ of the thyroglossal duct.—*Surg., Gynec. & Obst.*, Chicago, 1921, xxxii, 141-149.

VON GLAHN, W. C., and HERMAN, N. B.
Carcinoma of the supra-ampullary portion of the duodenum.—*Am. J. M. Sc.*, Phila., 1921, clxi, 111-119.

GODDARD, C. H.
The recognition and treatment of cardiac disorders.—*Tr. M. Ass. Alabama*, 1921.

GOETSCH, E.
The diagnosis and treatment of hyperthyroidism.—*N. York M. J.*, [etc.], 1921, cxiii, 378-383.
Hyperthyroidism in pregnancy.—*N. Y. State J. M.*, N. Y., 1921, xxi, 317-324.

GOODPASTURE, E. W.
Myocardial necrosis in hyperthyroidism.—*J. Am. M. Ass.*, Chicago, 1921, lxxvi, 1545-1551.
The influence of thyroid products on the production of myocardial necrosis.—*J. Exper. M.*, Balt., 1921, xxxiv, 407-423.

GOODPASTURE, E. W., and TALBOT, F. B.
Concerning the nature of "protozoan-like" cells in certain lesions of infancy.—*Am. J. Dis. Child.*, Chicago, 1921, xxi, 415-425.

GREENHILL, J. P.
A histological study of fetus and implantation site in a case of missed abortion.—*Am. J. Obst. & Gynec.*, St. Louis, 1921, ii, 188-194.
Tuberculous salpingitis. A clinical study of 200 cases.—*Johns Hopkins Hosp. Rep.*, Balt., 1921, xxi, 97-156.

GUNDRUM, F. F.
Focal infection.—*Calif. State J. M.*, San Fran., 1921, xix, 296.
Skin rashes in exophthalmic goitre.—*Calif. State J. M.*, San Fran., 1921, xix, 339.

GUTHRIE, C. G.
A simple and accurate metabolism spirometer. Spirometer measurement of oxygen consumption by the rebreathing method.—*Arch. Int. Med., Chicago*, 1921, xxviii, 687-702.

GWYN, N. B.
The epidemiology and diagnosis of encephalitis lethargica.—*Canad. M. Ass. J.*, Toronto, 1921, xi, 169-173.

HALSTED, W. S.
Ablation d'un anévrysme de la première portion de l'artère sous-clavière gauche.—*Lyon chirurg.*, 1921, xviii, 1-6.

HANSON, H.
Sanitary conditions in Peru.—*Am. J. Pub. Health*, N. Y., 1921, xi, 13-16.

HARROP, G. A., KROGH, A., and VON LIEBERMANN, P.
Studies on the physiology of capillaries. 11. The reactions to local stimuli of the blood-vessels in the skin and web of the frog.—*J. Physiol.*, Cambridge, 1921, lv, 412-422.

HASTREITER, R. F.
Nitrous oxide oxygen, analgesia and anesthesia in obstetrics.—*South. Calif. Pract.*, Los Angeles, 1921, xxxvi, 17-18.

HAZEN, H. H.
The diagnosis of syphilis.—*Am. J. Syph.*, St. Louis, 1921, v, 472-475.
Public health activities in venereal disease control.—*Am. J. Syph.*, St. Louis, 1921, v, 674-676.
Roentgen-ray treatment of cutaneous cancer.—*J. Am. M. Ass.*, Chicago, 1921, lxxvi, 1222-1227.

HENDERSON, D. K.
War psychoses, the infective, exhaustive group.—*Glasgow M. J.*, 1921, xcvi, 321-336.

HENNINGTON, C. W.
Abdominal incision.—*N. York State J. M.*, N. Y., 1921, xxi, 81-83.

HERMAN, N. B., and VON GLAHN, W. C.
Carcinoma of the supra-ampullary portion of the duodenum.—*Am. J. M. Sc.*, Phila., 1921, clxi, 111-119.

HEUER, G. J.
Surgery of the thorax.—*In:* Surgery, its Principles & Practice. (Keen) Phila. & Lond., 1921, viii, 332-414.

HIGGINS, W. H.
Unusual relapse in typhoid fever.—*Virginia M. Month.*, Richmond, 1921-22, xlviii, 347-348.

HINMAN, F.
Multiple renal and ureteral stones in an infant of eleven months; with results of ureteronephrectomy.—*J. Am. M. Ass.*, Chicago, 1921, lxxvi, 237-238.

HINMAN, F., and GIBSON, T. E.
Squamous cell carcinoma of the bladder: a study of heterotopic epidermization, with a review of the literature and report of cases.—*J. Urol.*, Balt., 1921, vi, 1-50.

HIRSCHFELDER, A. D.
Saligenin, a new non-toxic local anesthetic and its mercury derivative, a new antiseptic.—*Minnesota Med.*, St. Paul, 1921, iv, 399-402.

HIRSCHFELDER, A. D., HART, M. C., and KUCERA, F. J.
Mercury saligenin, a new antiseptic.—*Proc. Soc. Exper. Biol. & Med.*, N. Y., 1920-21, xviii, 77-79.

HIRSCHFELDER, D., HART, M. C., and KUCERA, F. J.
Further studies on saligenin: its mercury derivative and allied compounds. (Proceedings.)—*J. Pharmacol. & Exper. Therap.*, Balt., 1921, xvii, 325-326.

HIRSCHFELDER, D., and QUIGLEY, J. P.
The relation of substitution in the carbinol group to the pharmacological action of some phenyl carbinols (Proceedings).—*J. Pharmacol. & Exper. Therap.*, Balt., 1921, xvii, 326-327.

HITZROT, J. M.
Fractures of the head and the neck of the radius.—*Am. J. Surg.*, N. Y., 1921, xxxv, 100-109.

HITZROT, J. M., and MURRAY, C. R.
The factors that influence the prognosis in fractures at the base of the radius.—*Am. J. Surg.*, N. Y., 1921, xxxv, 17-29.

HITZROT, J. M., and WEEDEN, W. M.
The treatment of acute suppurative pleurisy.—*Ann. Surg.*, Phila., 1921, lxxiii, 531-544.

HOHMAN, L. B.
Epidemic encephalitis (lethargic encephalitis) its psychotic manifestations, with a report of twenty-three cases.—*Arch. Neurol. & Psychiat.*, Chicago, 1921, vi, 295-333. *Also:* [Abstr.] Maryland Psychiat. Q., Balt., 1921, x, 73-77.

HOLMES, J. B.
Recent progress in anatomy, physiology and pathology of childhood.—*Am. J. Dis. Child.*, Chicago, 1921, xxii, 61-103.

HOLMES, W. R.
The illness and death of Napoleon.—*J. Med. Ass. Georgia*, Atlanta, 1921, x, 628.

HOSKINS, R. G.
Some current trends in endocrinology.—*J. Am. M. Ass.*, Chicago, 1921, lxxvii, 1459-1462.
The reaction to epinephrin administered by rectum.—*J. Pharmacol. & Exper. Therap.*, Balt., 1921, xviii, 207-211.

HOSKINS, R. G., and EBAUGH, F. G.
A case of dystrophia adiposogenitalis.—*Endocrinology*, Glendale, Cal., 1921, v, 21-28.

HOWARD, C. P.
Obesity.—*In:* Oxford Med., 1921, iv, 195-213.
Hemochromatosis.—*In:* Oxford Med., 1921, iv, 215-222.
Ochronosis.—*In:* Oxford Med., 1921, iv, 223-228.
Rickets.—*In:* Oxford Med., 1921, iv, 229-252.
Scurvy.—*In:* Oxford Med., 1921, iv, 253-272.
Treatment of pneumonia with special reference to the use of serum.—*Canad. M. Ass. J.*, Toronto, 1921, xi, 709-713.

HOWARD, C. P., and GIBSON, R. B.
A case of alkaptonuria with a study of its metabolism.—*Arch. Int. Med.*, Chicago, 1921, xxviii, 632-637.

HOWELL, W. H.
Dr. Meltzer's influence on American physiology.—*Proc. Soc. Exper. Biol. & Med.*, N. Y., 1920-21, xviii, 25-36. Memorial Number for S. J. Meltzer.
Samuel James Meltzer.—*Science*, N. Y. & Lancaster, 1921, liii, 99-106.

HOWLAND, J.
Prolonged intolerance to carbohydrates. (Proceedings.)—*Arch. Pediat.*, N. Y., 1921, xxxviii, 393-396.
Measles.—*In:* Oxford Med., 1921, v, 499-517.
Scarlet fever.—*In:* Oxford med., 1921, v, 519-546.
Rubella.—*In:* Oxford med., 1921, v, 547-551.

HOWLAND, J., and KRAMER, B.
Calcium and phosphorus in the serum in relation to rickets.—*Am. J. Dis. Child.*, Chicago, 1921, xxii, 105-119.

HOWLAND, J., KRAMER, B., and TISDALL, F. F.
Observations on infantile tetany.—*Am. J. Dis. Child.*, Chicago, 1921, xxii, 431-437.
The clinical significance of calcium concentration in the serum of children and possible errors in its determination.—*Am. J. Dis. Child.*, Chicago, 1921, xxii, 560-564.

HOWLAND, J., TISDALL, F. F., and KRAMER, B.
The concentration of sodium and potassium as compared with that of calcium and magnesium in the serum of patients with active infantile tetany.—*Proc. Soc. Exper. Biol. & Med.*, N. Y., 1921, xviii, 252-253.

HUGHSON, W., and WEED, L. H.
The skull as a closed box. (Proceedings.) *Anat. Record*, Phila., 1921, xxi, 88.

HUNNER, G. L.
Intractable bladder symptoms due to ureteritis.—*Tr. Am. Urol. Ass.*, 1920, Balt., 1921, xii, 193-219.

HUNT, R.
Some factors relating to the toxic action of arsphenamin.—*J. Am. M. Ass.*, Chicago, 1921, lxxvi, 854-859.

HURD, H. M.
The early days of the Training School for Nurses at the Johns Hopkins Hospital.—*Johns Hopkins Nurses Alumnae Mag.*, Balt., 1921, xx, 63-71.

HURWITZ, S. H.
Some aspects of pernicious anemia and its treatment.—*Calif. State J. M.*, San Fran., 1921, xix, 275.

INGRAHAM, C. B.
Impresssions gained from the use of radium during the past year.—*Colorado Med.*, Denver, 1921, xviii, 72-75.
Vaginal cysts.—*J. Am. M. Ass.*, Chicago, 1921, lxxvii, 1487-1489.

JEIDELL, HELMINA.
Active immunization against diphtheria.—*Northwest Med.*, Seattle, 1921, xx, 89-92.

JOSEPHS, H. W., and DAVISON, W. C.
The serotherapy of bacillary dysentery in children.—*J. Am. M. Ass.*, Chicago, 1921, lxxvii, 1863-1864.

KEIDEL, A.
The treatment of neurosyphilis.—*South. M. J.*, Birmingham, Ala., 1921, xiv, 595-601.

KEIDEL, A., and MOORE, J. E.
Internal hydrocephalus in a syphilitic, probably due to intraspinal treatment.—*Am. J. M. Sc.*, Phila., 1921, clxii, 209-215.
Stomatitis and aplastic anemia due to neoarsphenamin.—*Arch. Dermatol. & Syph.*, Chicago, 1921, iv, 169-176.
Dermatitis and allied reactions following the arsenical treatment of syphilis.—*Arch. Int. Med.*, Chicago, 1921, xxvii, 716-747.
Comparative results of colloidal mastic and colloidal gold tests.—*Arch. Neurol. & Psychiat.*, Chicago, 1921, vi, 163-172.
Studies in asymptomatic neurosyphilis. I. A tentative classification of early asymptomatic neurosyphilis.—*Arch. Neurol. & Psychiat.*, Chicago, 1921, vi, 286-291.
Studies in familial neurosyphilis. 1. Conjugal neurosyphilis.—*J. Am. M. Ass.*, Chicago, 1921, lxxvii, 1-7.

KELLY, H. A.
Lafayette Houghton Bunnell, M. D., discoverer of the Yosemite.—*Ann. Med. Hist.*, N. Y., 1921, iii, 179-193.
Operation for renal calculi.—*N. York M. J.*, [etc.], 1921, cxiii, 1-3.
Drainage in pelvic abdominal surgery.—*N. York M. J.* [etc.], 1921, cxiv, 391-394.
The treatment with radium of cancer of the bladder. (Correspondence.)—*Surg., Gynec. & Obst.*, Chicago, 1921, xxxii, 187.
A diary of Robert Battey, M. D.—*Therap. Gaz.*, Detroit, 1921, xlv, 612-620. *Also: J. Med. Ass. Georgia*, Atlanta, 1921, x, 693-695.
Uterine polyps.—*Therap. Gaz.*, Detroit, 1921, xlv, 761-767.

KELLY, H. A., and FRICKE, R. E.
The use of pessaries.—*Therap. Gaz.*, Detroit, 1921, xlv, 5-9.

KETRON, L. W.
A note on the treatment of larva migrans.—*Arch. Dermatol. & Syphil.*, Chicago, 1921, iv, 368-369.

KEMPF, E. J.
A minimum course in psychopathology for medical students.—*N. York M. J.* [etc.], 1921, cxiii, 309-313.

KEMPF, HELEN C.
Child health, the nation's wealth.—*Woman Citizen*, N. Y., August, 1921.

KLINE, B. S.
Spirochetal pulmonary gangrene.—*J. Am. M. Ass.*, Chicago, 1921, lxxvii, 1874-1877.

KLINE, B. S., and FISHBERG, M.
Spirochetal pulmonary gangrene.—*Arch. Int. Med.*, Chicago, 1921, xxvii, 61-70.

KNOX, J. H. M., JR.
The health center, what it may mean to a community. (Proceedings.)—*Arch. Pediat.*, N. Y., 1921, xxxviii, 451.
The claim of the child.—*Bambino*, Columbus, Ohio, 1921, 10-11.
Erysipelas in childhood.—*South. M. J.*, Birmingham, Ala., 1921, xiv, 387-393.

KRAMER, B., and HOWLAND, J.
Calcium and phosphorus in the serum in relation to rickets.—*Am. J. Dis. Child.*, Chicago, 1921, xxii, 105-119.

KRAMER, B., and TISDALL, F. F.
A clinical method for the quantitative determination of potassium in small amounts of serum.—*J. Biol. Chem.*, Balt., 1921, xlvi, 339-349.
Simple method for the direct quantitative determination of sodium in small amounts of serum.—*J. Biol. Chem.*, Balt., 1921, xlvi, 467-473.
A simple technique for the determination of calcium and magnesium in small amounts of serum.—*J. Biol. Chem.*, Balt., 1921, xlvii, 475-481.
Methods for the direct quantitative determination of sodium, potassium, calcium, and magnesium in urine and stools.—*J. Biol. Chem.*, Balt., 1921, xlviii, 1-12.
The direct quantitative determination of sodium, potassium, calcium, and magnesium in small amounts of blood.—*J. Biol. Chem.*, Balt., 1921, xlviii, 223-232.

KRAMER, B., TISDALL, F. F., and HOWLAND, J.
Observations on infantile tetany.—*Am. J. Dis. Child.*, Chicago, 1921, xxii, 431-437.
The clinical significance of calcium concentration in the serum of children and possible errors in its determination.—*Am. J. Dis. Child.*, Chicago, 1921, xxii, 560-564.
The concentration of sodium and potassium as compared with that of calcium and magnesium in the serum of patients with active infantile tetany.—*Proc. Soc. Exper. Biol. & Med.*, N. Y., 1921, xviii, 252-253.

KRAUSE, A. K.
Tuberculosis: infection, pathology, etiology and bacteriology.—*In:* Nelson Loose-Leaf Med., Lond. & N. Y., [1921], i, 309-336.
Some problems of medical education in tuberculosis.—*Am. Rev. Tuberc., Balt.*, 1921-22, v, 755-768.
The tuberculosis problem. Some thoughts on its solution.—*Am. Rev. Tuberc.*, Balt., 1921-22, v, 769-763.
Essays on tuberculosis. xx. Some phases of resistance. Part iv. Immunity. (Continued.) Immunization with living virulent bacilli: Trudeau's work.—*J. Outdoor Life*, N. Y., 1921, xviii, 31-34; 48-49.
Essays on tuberculosis. xx. Some phases of resistance. Part iv. Immunity. (Continued.) Cattle immunization.—*J. Outdoor Life*, N. Y., 1921, xviii, 63-67.
Essays on tuberculosis. xxi. Some phases of resistance. Part iv. (Immunity, concluded.) The nature of resistance: its determining factors.—*J. Outdoor Life*, N. Y., 1921, xviii, 247-252.
Essays on tuberculosis. xxii. Reinfection.—*J. Outdoor Life*, N. Y., 1921, xviii, 278-286.
Essays on tuberculosis. xxiii. The elementary pathology of tuberculosis.—*J. Outdoor Life*, N. Y., 1921, xviii, 305-312; 327.
Essays on tuberculosis. xxiv. The pathology of tuberculosis: its spread throughout the body.—*J. Outdoor Life*, N. Y., 1921, xviii, 342-347; 358-359.
Course of tubercle bacillus from sputum to the child.—*N. Y. State J. M.*, N. Y., 1921, xxi, 83.
Enseignement de la tuberculose aux étudiants. Mission Américaine de préservation contre la Tuberculose (Fondation Rockefeller), Paris, 1921.
Tuberculin: its nature and its effects on tuberculous animals; its action. Bureau of Correspondence and information, Texas State Tuberculosis Sanatorium, 1920. Pamphlet No. 22. [1921.] 23 p. 8°.

LEONARD, V. N.
A building designed to meet the requirements of group practice.—*Mod. Hosp.*, St. Louis, 1921, xvii, 131-132.

LEVY, R. L.
Advanced heart failure. General symptoms.—*In:* Nelson Loose-Leaf Med., 1921, iv, 285-300.
Restoration of the normal cardiac mechanism in auricular fibrillation by quinidin. Preliminary report.—*J. Am. M. Ass.*, Chicago, 1921, lxxvi, 1289-1293.

LEVY, R. L., and COHN, A. E.
Experimental studies of the pharmacology of quinidin.—*Proc. Soc. Exper. Biol. & Med.*, N. Y., 1920-21, xviii, 283-284.

LEWIS, D. S., and MOFFATT, C. F.
Standardization of certain preparations of digitalis.—*Canad. M. Ass. J.*, Toronto, 1921, xi, 755-758.

LEWIS, W. H., and WEBSTER, L. T.
Migration of lymphocytes in plasma cultures of human lymph nodes.—*J. Exper. M.*, Balt., 1921, xxxiii, 261-269.
Giant cells in cultures from human lymph nodes.—*J. Exper. M.*, Balt., 1921, xxxiii, 349-360.
Wandering cells, endothelial cells, and fibroblasts in cultures from human lymph nodes.—*J. Exper. M.*, Balt., 1921, xxxiv, 397-406.

LINTHICUM, F. H.
Ozena and its relation to tuberculosis.—*Am. J. M. Sc.*, Phila., 1921, clxii, 216-226.

LISSER, H.
Does the pituitary secretion influence the development of the prostate?—*N. York M. J.*, [etc.], 1921, cxiii, 391-393.

LITTLE, H. M.
The least common multiple in obstetrics.—*Am. J. Obst. & Gynec.*, St. Louis, 1921, ii, 67-76.

LOWSLEY, O. S.
The rôle of the prostate and seminal vesicles in arthritis. With a discussion of surgical and nonsurgical treatment.—*N. York M. J.*, [etc.], 1921, cxiii, 641-646. *Also: Tr. Am. Urol. Ass.*, 1920, Balt., 1921, xii, 1-18.
A perineal operation for removal of stone in the lower end of the male ureter.—*Surg., Gynec. & Obst.*, Chicago, 1921, xxxii, 300-306.

LYMAN, D. R.
The limitations and possibilities in the federal care of tuberculous ex-service patients.—*Nat. Tubere. Ass., Tr.*, N. Y., 1921, xvii.

MACCALLUM, W. G.
The pathology of the pneumonia in the United States army camps during the winter of 1917-18.—*Johns Hopkins Hosp. Rep.*, Balt., 1921, xx, 1-147.
Pathological anatomy of pneumonia associated with influenza.—*Johns Hopkins Hosp. Rep.*, Balt., 1921, xx, 149-249.

MACCALLUM, W. G., and MOODY, L. M.
Alastrim in Jamaica.—*Am. J. Hyg.*, Balt., 1921, i 388-409.

MCCANN, W. S.
The effect of the ingestion of foodstuffs on the respiratory exchange in pulmonary tuberculosis.—*Arch. Int. Med.*, Chicago, 1921, xxviii, 847-858.
Limitations of metabolism determinations in diagnosis.—*Med. Clin. N. Am.*, Phila., 1921, iv, 1483.

MCCRAE, T.
Arthritis deformans.—*In: Oxford Med.*, 1921, iv, 367-403.
Pain in lower back.—*Med. Clin. N. Am.*, Phila., 1921, iv, 973.

MACHT, D. I.
On the absorption of local anesthetics through the genito-urinary organs.—*J. Pharmacol. & Exper. Therap.*, Balt., 1920-21, xvi, 435-448.
Pharmacological examination of cinnamein, benzyl succinate and benzyl nitrite.—*Proc. Soc. Exper. Biol. & Med.*, N. Y., 1920-21, xviii, 177-179.

MACHT, D. I., and BLOOM, W.
Experimental inquiry into the cerebral and neuromuscular manifestations of digitalis.—*Arch. Int. Med.*, Chicago, 1921, xxviii, 678-686.
Physiological and pharmacological studies of the prostate gland. III. Effect of prostatectomy on the behavior of albino rats.—*J. Urol.*, Balt., 1921, v, 29-41.
A pharmacodynamic analysis of cocain action of the cerebrum.—*Proc. Soc. Exper. Biol. & Med.*, N. Y., 1920-21, xviii, 81-82.
Comparative study of ethanol, caffeine and nicotine on behavior of albino rats.—*Proc. Soc. Exper. Biol. & Med.*, N. Y., 1920-21, xviii, 99-100.
The effect of prostatectomy on the behavior and learning of albino rats.—*Proc. Soc. Exper. Biol. & Med.*, N. Y., 1920-21, xviii, 100-101.
Comparative study of ethanol, caffeine and nicotine on the development of frogs' larvæ.—*Proc. Soc. Exper. Biol. & Med.*, N. Y., 1920-21, xviii, 241-242.

MACHT, D. I., and TING, G. C.
Response to drugs of excised bronchi from normal and diseased animals.—*J. Pharmacol. & Exper. Therap.*, Balt., 1921, xviii, 111-119.
Experimental inquiry into sedative properties of some aromatic drugs and fumes.—*J. Pharmacol. & Exper. Therap.*, Balt., 1921, xviii, 361.
Effect of antispasmodic drugs on bronchus.—*J. Pharmacol. & Exper. Therap.*, Balt., 1921, xviii, 373.

MAJOR, R. H.
The treatment of empyema with gentian violet.—*Am. J. M. Sc.*, Phila., 1921, clxii, 397-406.

MARRIOTT, W. MCK.
Abnormal metabolism in infancy and its relationship to symptomatology.—*Brit. J. Child. Dis.*, Lond., 1921, xviii, 129-135.

MARSHALL, H. W.
Scoliosis.—*Boston M. & S. J.*, 1921, clxxxiv, 31-40.
When to open knee-joints.—*Boston M. & S. J.*, 1921, clxxxiv, 291-297.
A case of myositis ossificans traumatica developing from torn coracoclavicular ligament without other bony fracture.—*Boston M. & S. J.* 1921, clxxxiv, 380-384.
A questionnaire on sacro-iliac joint lesions.—*Boston M. & S. J.*, 1921, lxxxv, 79-88.
Restaurant treatment in industrial accident cases (Correspondence).—*J. Am. M. Ass.*, Chicago, 1921, lxxvii, 1273.

MASON, C. C., and SHOHL, A. T.
Food at the front lines.—*Mil. Surgeon, Wash.*, 1921, xlviii, 386-401.

MAXWELL, J. P.
Obstetrics and gynecology in South China.—*China M. J.*, Shanghai, 1921, xxxv, 146-154.
Intestinal parasitism in South Fukien.—*China M. J.*, Shanghai, 1921, xxxv, 377-382.

MEYER, A.
The contributions of psychiatry to the understanding of life problems.—*In:* A Psychiatric Milestone. Bloomingdale Hospital Centenary 1821-1921. N. Y., 1921, 21-54. [Privately printed.]
The integrative function of a hospital laboratory. Retrospect and prospect.—*State Hosp. Q.*, Utica, N. Y., 1921, vi, 445-451.
Psychopathology. By E. J. Kemp. St. Louis, 1920, C. V. Mosby Co. 762 p. 8°. (Book review.)—*Arch. Neurol. & Psychiat.*, Chicago, 1921, v, 782-790.
Medizin und Recht. Die Beziehungen der Medizin zum Recht, die Kausalität in Medizin und Recht und die Aufgaben des gerichtlich-medizinischen Unterrichtes, von Prof. H. Zangger. Art. Institut Orell Füssli. (Book review.)—*J. A. Inst. . . . Criminol.*, Chicago, 1921-22, xii, 457-458.

MILLER, M. K.
Splenic anemia of infancy, with report of a case occurring in an infant at six weeks of age.—*Arch. Pediat.*, N. Y., 1921, xxxviii, 11-17.
Polyneuritic syndrome in young children.—*J. Indiana M. Ass.*, Fort Wayne, 1921, xiv, 144-145.

MILLER, M. K., and LYON, M. W., JR.
Case of meningitis in an infant due to a thread-like diphtheroid organism.—*Am. J. M. Sc.*, Phila., 1921, clxii, 593-598.

MILLS, R. G.
Abstract of Japanese medical literature.—*China M. J.*, Shanghai, 1921, xxxv, 67-78; 171-180.
Pathological specimens (Correspondence).—*China M. J.*, Shanghai, 1921, xxxv, 185-186.
A preliminary study of post-operative catheterization.—*China M. J.*, Shanghai, 1921, xxxv, 217-241.
A study of post-operative catheterization in Korea.—*China M. J.*, Shanghai, 1921, xxxv, 310-331.
Ecological studies in the Tang-Mai River basin, North Korea.—*Tr. Korea Branch Royal Asiatic Soc.*, 1921, xii, part 1.

MINOT, G. R.
Two curable cases of anemia.—*Med. Clin. N. Am.*, Phila., 1921, iv, 1733-1750.

MINOT, G. R., and SMITH, L. W.
The blood in tetrachlorethane poisoning.—*Arch. Int. Med.*, Chicago, 1921, xxviii, 687-702.

MOORE, J. E.
The genesis of neurosyphilis.—*Arch. Dermatol. & Syph.*, Chicago, 1921, iv, 55-61.
The cerebrospinal fluid in treated syphilis.—*J. Am. M. Ass.*, Chicago, 1921, lxxvi, 769-773.

MOORE, J. E., and KEIDEL, A.
Internal hydrocephalus in a syphilitic, probably due to intraspinal treatment.—*Am. J. M. Sc.*, Phila., 1921, clxii, 209-215.
Stomatitis and aplastic anemia due to neo-arsphenamin.—*Arch. Dermatol. & Syph.*, Chicago, 1921, iv, 169-176.
Dermatitis and allied reactions following the arsenical treatment of syphilis.—*Arch. Int. Med.*, Chicago, 1921, xxvii, 716-747.
Comparative results of colloidal mastic and colloidal gold tests.—*Arch. Neurol. & Psychiat.*, Chicago, 1921, vi, 163-172.
Studies in asymptomatic neurosyphilis. I. A tentative classification of early asymptomatic neurosyphilis.—*Arch. Neurol. & Psychiat.*, Chicago, 1921, vi, 286-291.
Studies in familial neurosyphilis. 1. Conjugal neurosyphilis.—*J. Am. M. Ass.*, Chicago, 1921, lxxvii, 1-7.

MORRIS, R. S.
Some difficulties in the diagnosis of empyema complicating pneumonia.—*J. Am. M. Ass.*, Chicago, 1921, lxxvi, 1336-1337.
A simple and inexpensive apparatus for diagnostic or therapeutic punctures.—*J. Am. M. Ass.*, Chicago, 1921, lxxvii, 286.

MOSENTHAL, H. O.
Diabetes mellitus. A system of diets. With list of diets in pad form (50 sheets in a pad).—N. Y., 1921. P. B. Hoeber.
The clinical value of basal metabolism determinations in diseases of the thyroid glands.—*N. York M. J.*, [etc.], 1921, cxiv, 41-43.

MOSENTHAL, H. O., and MARKS, H. E.
The clinical value of basal metabolism.—*Med. Clin. N. Am.*, Phila., 1921, iv, 1403.

NIXON, P. I.
Congenital hypertrophic pyloric stenosis in infants.—*Med. Rec.*, N. Y., 1921, xcix, 433-435.
Acute dilatation of the stomach following gynecological operations.—*Texas State J. M.*, Fort Worth, 1921, xvi, 481-483.

NORRIS, C. C.
Gynecological and obstetrical tuberculosis.—N. Y., 1921, D. Appleton & Co. 348 p. 8°.
Ovary containing endometrium.—*Am. J. Obst. & Gynec.*, St. Louis, 1920-21, i, 831-834.
The treatment of gonorrhœa in the lower genito-urinary tract in women.—*Surg., Gynec. & Obst.*, Chicago, 1921, xxxiii, 308-311.

NOVAK, E.
Menstruation and its disorders.—N. Y. & Lond., 1921, D. Appleton & Co., 357 p. 8°.
Acute postoperative dilatation of the stomach.—*J. Am. M. Ass.*, Chicago, 1921, lxxvii, 81-88.
[The interpretation and clinical significance of uterine hæmorrhage.]—*Med. Weekbl.*, Amst., 1921, xxvii, 563-573.

NUTTALL, G. H. F., and KEILIN, D.
On the nephrocytes of *Pediculus humanus*.—*Parasitology*, Cambridge, 1921, xiii, 184-192.

OPIE, E. L., RIVERS, T. M. [*et al.*]
Epidemic respiratory diseases. The pneumonias and other infections of the respiratory tract accompanying influenza and measles. St. Louis, 1921, C. V. Mosby Co., 402 p. 8°.

OLIVER, J. R.
The results of the application of laboratory methods to the study of delinquency. Read at Ann. Cong. Am. Prison Assoc., Columbus, Ohio.—*Proc. Am. Prison Assoc.*, 1921.
Emotional states and illegal acts in connection with schizophrenia.—*Proc. Am. Psychiat. Assoc.*, 1921.
The causes and cures of crime. By Thomas S. Mosby. St. Louis. 1913, C. V. Mosby Co., 354 p. 8°.—*Ment. Hyg.*, N. Y., 1921, v, 873-876.
Modern criminal procedure in Switzerland. By Prof. Hafter, of Zurich. [Transl. and comments.]—*J. Am. Inst. . . . Criminol.*, Chicago, 1921-22, xii.

PALMER, W. W.
Metabolism. (Survey of literature from Sept. 1, 1920, to March 1, 1921.)—*In:* Nelson Loose-Leaf Med., Lond. & N. Y., 1921, iii, 36.
Diabetes insipidus. (Survey of literature from Sept. 1, 1920, to March 1, 1921.)—*In:* Nelson Loose-Leaf Med., Lond. & N. Y., 1921, iii, 54-55.

PALMER, W. W., ATCHLEY, D. W., and LOEB, R. F.
Studies on the regulation of osmotic pressure. I. The effect of increasing concentrations of gelatin on the conductivity of sodium chloride solution.—*J. Gen. Physiol.*, Balt., 1921, iii, 801-806.

PALMER, W. W., and JACKSON, H., JR.
A modification of Folin's uric acid method.—*Proc. Soc. Exper. Biol. & Med.*, N. Y., 1920-21, xviii, 126-127.

PALMER, W. W., and LADD, W. S.
The carbohydrate fat ratio in relation to the production of ketone bodies in diabetes mellitus.—*Proc. Soc. Exper. Biol. & Med.*, N. Y., 1920-21, xviii, 109-110.

PARFITT, C. D.
Summary of report. Board of Tuberculosis Consultants. Dept. Soldiers' Civil Re-Establishment.—Ottawa, Canada, 1921, 21 p. 8°.
Experiences in classification of sanatoria.—*Nat. Tuberc. Ass., Tr.*, N. Y., 1921, xvii.
Extensive rib resection in the treatment of pulmonary tuberculosis. Report of 4 cases.—*Tr. Am. Climat. & Clin. Ass.*, Phila., 1921, xxxvii.

PARK, E. A., MCCOLLUM, E. V., SIMMONDS, NINA, and SHIPLEY, P. G.
Studies on experimental rickets. IV. Cod-liver oil as contrasted with butter fat in the protection against the effects of insufficient calcium in the diet.—*Proc. Soc. Exper. Biol. & Med.*, N. Y., 1920-21, xviii, 275-277.

PARK, E. A., SHIPLEY, P. G., MCCOLLUM, E. V., and SIMMONDS, NINA.
Studies on experimental rickets. V. The production of rickets by means of a diet faulty in only two respects.—*Proc. Soc. Exper. Biol. & Med.*, N. Y., 1920-21, xviii, 277-280.

PARK, E. A., MCCOLLUM, E. V., SIMMONDS, NINA, and SHIPLEY, P. G.
Studies on experimental rickets. VI. The effects on growing rats of diets deficient in calcium.—*Am. J. Hyg.*, Balt., 1921, i, 492-511.

PARK, E. A., SHIPLEY, P. G., MCCOLLUM, E. V., and SIMMONDS, NINA.
Studies on experimental rickets. VII. The relative effectiveness of cod liver oil as contrasted with butter fat protecting the body against insufficient calcium in the presence of a normal phosphorus supply.—*Am. J. Hyg.*, Balt., 1921, i, 512-525.

PATON, S.
Human behavior, in relation to the study of educational, social, and ethical problems. N. Y., 1921, C. Scribner's Sons. 465 p. 8°.

PEABODY, F. W.
Acute poliomyelitis.—*In:* Oxford Med., 1921, v, 107-123.
A report of the Harvard Infantile Paralysis Commission on the diagnosis of acute cases in 1920; with special reference to the incidence of cases without paralysis.—*Boston M. & S. J.*, 1921, clxxxv, 174-176.
The vital capacity of the lungs in heart disease.—*Med. Clin. N. Am.*, Phila., 1921, iv, 1655-1671.

PEABODY, F. W., and STURGIS, C. C.
Clinical studies of the respiration. vii. The effect of general weakness and fatigue on the vital capacity of the lungs.—*Arch. Int. Med.*, Chicago, 1921, xxviii, 501-510.

PEABODY, F. W., STURGIS, C. C., TOMPKINS, E. M., and WEARN, J. T.
Epinephrin hypersensitiveness and its relation to hyperthyroidism.—*Am. J. M. Sc.*, Phila., 1921, clxi, 508-517.

PEARCE, LOUISE.
Studies on the treatment of human trypanosomiasis with tryparsamide (the sodium salt of N-phenylglycineamide-p-arsonic acid).—*J. Exper. M.*, Balt., 1921, xxxiv, 1-104. (Suppl. No. 1.)

PEARCE, LOUISE, and BROWN, W. H.
Latent infections with the demonstration of *Spirochete pallida* in lymphoid tissues of the rabbit.—*Am. J. Syph.*, St. Louis, 1921, v, 1-8.
Experimental production of clinical types of syphilis in the rabbit.—*Arch. Dermatol. & Syph.*, Chicago, 1921, n. s., iii, 254-262.
The defensive reactions of animals infected with *Spirochaeta pallida*.—*J. Am. M. Ass.*, Chicago, 1921, lxxvii, 1619-1620.
Therapeutic action of N-phenylglycineamide-p-arsonic acid (tryparsamide) upon experimental infections of Trypanosoma rhodesiense.—*J. Exper. M.*, Balt., 1921, xxxiii, 193-200.
Superinfection in experimental syphilis following the administration of subcurative doses of arsphenamine or neoarsphenamine.—*J. Exper. M.*, Balt., 1921, xxxiii, 553-567.
Experimental syphilis in the rabbit. VII. Affections of the eyes.—*J. Exper. Med.*, Balt., 1921, xxxiv, 167-183.
Note on the preservation of the stock strains of *Treponema pallidum* and on the demonstration of infection in rabbits.—*J. Exper. Med.*, Balt., 1921, xxxiv, 185-188.
The penetration of normal mucous membranes of the rabbit by *Treponema pallidum*.—*Proc. Soc. Exper. Biol. & Med.*, N. Y., 1920-21, xviii, 200-201.
Neoplasia in experimental syphilis.—*Proc. Soc. Exper. Biol. & Med.*, N. Y., 1920-21, xviii, 201-202.
Superinoculation experiments with *Treponema pallidum*.—*Proc. Soc. Exper. Biol. & Med.*, N. Y., 1920-21, xviii, 255-257.
Multiple infections with *Treponema pallidum* in the rabbit.—*Proc. Soc. Exper. Biol. & Med., N. Y.*, 1920-21, xviii, 258-261.

PEARCE, LOUISE, BROWN, W. H., and WITHERBEE, W. D.
Experimental syphilis in the rabbit. VI. Affections of bone, cartilage, tendons, and synovial membranes. 1. Lesions of the skeletal system. 2. Clinical aspects of syphilis of the skeletal system. Affections of the facial and cranial bones and the bones of the forearm. 3. Syphilis of the posterior extremities with other affections of a miscellaneous type.—*J. Exper. M.*, Balt., 1921, xxxiii, 495-514; 515-524; 525-538.

PEARL, R.
The significance of biometry and vital statistics to the science of medicine.—*In:* Nelson Loose-Leaf Med., Lond. & N. Y., 1921, vii, 111-127.
The biology of death: I. The problem. II. Conditions of cellular immortality. III. The chances of death. IV. The cause of death. V. The inheritance of the duration of life in man. VI. Experimental studies on the duration of life. VII. Natural death, public health, and the population problem.—*Scient. Month.*, N. Y., 1921, xii, 193-214; 321-335; 443-456; 489-516. xiii, 46-66; 144-164; 193-213.
Influenza studies: II. Further data on the correlation of explosiveness of outbreak of the 1918 epidemic. III. On the correlation of destructiveness of the 1918 epidemic. IV. On the correlation between explosiveness and total destructiveness of the epidemic mortality.—*Pub. Health Rep.*, Wash., 1921, xxxvi, 273-298.
A further note on war and population.—*Science*, N. Y. & Lancaster, 1921, liii, 120-121.
Variation in the rate of infant mortality in the United States birth registration area.—*Tr. Am. Child Hyg. Ass.*, Balt., 1921, xi, 213-229.
Biometric data on infant mortality in the United States birth registration area, 1915-1918.—*Am. J. Hyg.*, Balt., 1921, i, 419-439.
A biological classification of the causes of death.—*Metron*, Rovigo, 1921, i, 92-99.

PEARL, R., and FAIRCHILD, T. E.
Studies on the physiology of reproduction in the domestic fowl. XIX. On the influence of free choice of food materials on winter egg production and body weight.—*Am. J. Hyg., Balt.*, 1921, i, 253-277.

PEARL, R., and KELLY, F. C.
Forecasting the growth of nations. The future population of the world and its problems.—*Harper's Mag.*, N. Y., 1921, cxliii, 704-713.

PEARL, R., and SCHOPPE, W. F.
Studies on the physiology of reproduction in the domestic fowl. xviii. Further observations on the anatomical basis of fecundity.—*J. Exper. Zool.*, Phila., 1921, xxxiv, 101-118.

PETERS, L.
Report of a case of large meningocele producing dystocia, delivery by Porro operation.—*Am. J. Obst. & Gynec.*, St. Louis, 1921, ii, 636-639.

PINCOFFS, M. C., and BOGGS, T. R.
Diseases of the peritoneum.—*In:* Oxford Med., 1921, iii, 517-581.

VON PIRQUET, C.
Children's diet. (Correspondence.)—*Lancet*, Lond., 1921, i, 558.
Der Begriff "Aequum."—*Ztschr. f. Kinderh.*, Berl., 1921, xxx, 145-146.

PLAGGEMEYER, H. W.
The medical aspect of prostatic surgery.—*Grace Hosp. Bull.*, Detroit, 1921, v, 1-7.

POST, L. T.
A study of the etiology of periodic ophthalmia in horses.—*Am. J. Ophth.*, Chicago, 1921, s. 3, iv, 330-333.
Quantitative determination of cocain and atropin absorption by aqueous humor.—*J. Am. M. Ass.*, Chicago, 1921, lxxvii, 1323-1324.

POST, L. T., and SHAHAN, W. E.
Thermophore studies in glaucoma.—*Am. J. Ophth.*, Chicago, 1921, s. 3, iv, 109-118.

PUTNAM, MARY.
A survey of the rural children of western Massachusetts.—*Commonwealth*, Bost., 1921, vii, No. 6.

PUTNAM, T. J., and WISLOCKI, G. B.
Absorption from ventricles in experimentally produced internal hydrocephalus.—*Am. J. Anat.*, Phila., 1921, xxix, 313.

QUINBY, W. C.
The transperitoneal approach to the kidney; its indications and limitations.—*J. Urol.*, Balt., 1921, vi, 135-143.
The pathology of the renal pelvis in two cases showing hematuria of the so-called essential type.—*Tr. Am. Urol. Ass., 1920*, Balt., 1921, xii, 234-241.

RANDALL, A.
Congenital valves of the posterior urethra.—*Am. Surg.*, Phila., 1921, lxxiii, 477-480.
Report of a vesical calculus weighing four pounds.—*Tr. Am. Urol. Ass., 1920*, Balt., 1921, xii, 53-56.
Giant vesical calculus.—*J. Urol.*, Balt., 1921, v, 119-125.
The varying types of prostatic obstruction.—*J. Urol.*, Balt., 1921, v, 287-308.

RANDALL, A., and MOORHEAD, S. W.
Sterilizer for cystoscopes.—*J. Urol.*, Balt., 1921, v, 265-266.

RANDALL, A., SMALL, J. C., and BELK, W. P.
Tropical inguinal granuloma in the Eastern United States.—*J. Urol.*, Balt., 1921, v, 539-548.

REICHERT, F. L.
On the fate of the primary lymph-sacs in the abdominal region of the pig, and the development of lymph-channels in the abdominal and pelvic regions.—*Contrib. Embryol.*, No. 58, (Carnegie Inst.), Wash., 1921, xiii, 17-39.

REID, M. R.
Drainage of the common bile duct through the cystic duct: cysticocholedochostomy.—*Ann. Surg.*, Phila., 1921, lxxiii, 458-469.

REYNOLDS, L., and MCCLURE, C. W.
Observations on the behavior of the normal pyloric sphincter in man.—*Am. J. Roentgenol.*, Detroit, 1921, viii, 158-162.

REYNOLDS, L., MCCLURE, C. W., and WETMORE, A. S.
New methods for estimating enzymatic activities of duodenal contents of normal man.—*Arch. Int. Med.*, Chicago, 1921, xxvii, 706-715.

RICH, A. R.
Condition of the capillaries in histamine shock.—*J. Exper. M.*, Balt., 1921, xxxiii, 287-298.

RICHARDS, ESTHER L.
Mental nursing.—*Johns Hopkins Nurses' Alumnae Mag.*, Balt., 1921, xx, 120-125.
The rôle of situation in psychopathological conditions.—*Ment. Hyg.*, N. Y., 1921, v, 449-467.
The elementary school and the individual child.—*Ment. Hyg.*, N. Y., 1921, v, 707-723.

RIGGS, T. F.
The Finney pyloroplasty.—*Journal-Lancet*, Minneapolis, 1921, xli, 517-522.

RIVERS, T. M.
Growth of influenza bacilli without blood.—*J. Am. M. Ass.*, Chicago, 1921, lxxvi, 1744-1745.

RIVERS, T. M., and KOHN, L. A.
The biological and the serological reactions of influenza bacilli producing meningitis.—*J. Exper. M.*, Balt., 1921, xxxiv, 477-494.

RIVERS, T. M., OPIE, E. L. [*et al.*]
Epidemic respiratory diseases. The pneumonias and other infections of the respiratory tract accompanying influenza and measles.—St. Louis, 1921, C. V. Mosby Co., 402 p. 8°.

ROBINSON, G. C.
Special symptoms of chronic diseases of the heart. Valvular disease.—*In:* Nelson Loose-Leaf Med., Lond. & N. Y., 1921, iv, 359-381.

ROBINSON, G. C., and HERMANN, G. R.
Paroxysmal tachycardia of ventricular origin, and its relation to coronary occlusion.—*Heart*, Lond., 1921-22, viii, 59-81.

ROSEN, R.
The physiopathology of the verumontanum.—*Urol. & Cutan. Rev.*, St. Louis, 1921, xxv, 26-30.

ROUS, P., and LARIMORE, LOUISE D.
Relation of the portal blood to liver maintenance. A demonstration of liver atrophy conditional on compensation.—*Stud. Rockefeller Inst. M. Research*, N. Y., 1921, xxxvi, 157-182.

ROUS, P., and MCMASTER, P. D.
The concentrating activity of the gall-bladder.—*J. Exper. M.*, Balt., 1921, xxxiv, 47-73.
Physiological causes for the varied character of stasis bile.—*J. Exper. M.*, Balt., 1921, xxxiv, 75-96.

ROUS, P., WILSON, G. W., and OLIVER, JEAN.
Experiments on the production of specific antisera for infections of unknown cause. III. The effects of a serum precipitin on animals of the species furnishing the precipitinogen.—*Stud. Rockefeller Inst. M. Research*, N. Y., 1921, xxxvi, 99-111.

ROWNTREE, L. G.
Diabetes insipidus.—*In:* Oxford Med., 1921, iv, 179-193.
The differential diagnosis of polyuria, with special reference to diabetes insipidus.—*Med. Clin. N. Am.*, Phila., 1921, v, 439-453.
The rôle and development of drug therapy.—*J. Am. M. Ass.*, Chicago, 1921, lxxvii, 1061-1065.
The spirit of investigation in medicine.—*Science*, N. Y. & Lancaster, 1921, liv, 179-183.

SAMPSON, J. A.
Perforating hemorrhagic (chocolate) cysts of the ovary. Their importance and especially their relation to pelvic adenomas of endometrial type ("adenomyoma" of the uterus, rectovaginal septum, sigmoid, etc.)—*Arch. Surg.*, Chicago, 1921, iii, 245-323.

SANGER, B. J.
The glucose mobilization rate in hyperthyroidism.—*Proc. Soc. Exper. Biol. & Med.*, N. Y., 1921, xviii, 117-120.

SCHLAEPFER, K.
Ueber einen weiteren Fall von Gallensteinileus.—*Beitr. z. klin. Chir.*, Tübing., 1921, cxxi, 122-135.
Ueber tödliche Nachblutungen nach Tracheotomie bei Larynxdiphtherie. —*Beitr. z. klin. Chir.* Tübing., 1921, cxxi, 212-227.
Die intrapleuralen Reflexe und ihre Bedeutung bei operativen Eingriffen.—*Ergebn. d. Chir. u. Orthop.*, Berl., 1921, xiv, 797-905.
Ueber die Behandlung der Analfistel und der Hämorrhoiden. (Beobachtungen am St. Mark-Spital in London).—*Med. Klin.*, Berl. & Wien, 1921, xvii, 1287-1289.
Reiseeindrücke eines Schweizerarztes an London's Spitälern. (Herbst 1920.) Briefe aus England.—*Schweiz. med. Wchnschr.*, Basel, 1921, li, 281-285; 302-306.

SEEM, R. B.
Relation of the dispensary to the Hospital.—*Mod. Hosp.*, St. Louis, 1921, xvi, 78-79.

SELLARDS, A. W.
Bacillary dysentery. *In:* Oxford Med., 1921, iv, 767-782.
Amebiasis.—*In:* Oxford med., 1921, v, 799-816.
Asiatic cholera. Survey of literature from Sept. 1, 1920, to March 1, 1921.—*In:* Nelson Loose-Leaf Med., Lond. & N. Y., 1921, ii, 104-105.

SELLARDS, A. W., and BIGELOW, G. H.
Investigation of the virus of measles.—*J. Med. Research*, Bost., 1921, xiii, 241-259.

SEXTON, L. A.
A new in and out registering device for the attending staff.—*Mod. Hosp.*, St. Louis, 1921, xvi, 552-553.
Selecting the personnel for the social service department.—*Mod. Hosp.*, St. Louis, 1921, xvii, 43-44.

SHARPE, W.
The pathology and treatment of chronic brain injuries, with and without a fracture of the skull.—*Am. J. Surg.*, N. Y., 1921, xxxv, 147-152.
Observations regarding the diagnosis and treatment of brain tumors.—*Internat. Clin.*, Phila., 1921, 31. s., ii, 227-240.
Observations regarding the surgical treatment of selected cases of purulent meningitis.—*Med. Rec.*, N. Y., 1921, c, 709-713.
Medical impressions of South America.—*Med. Rec.*, N. Y., 1921, c, 1062-1065.

SHAW, H. N.
A short account of the deaths occurring in the gynecologic service of the Johns Hopkins Hospital during the year 1919.—*Arch. Surg.*, Chicago, 1921, ii, 535-541.

SHIPLEY, A. M.
A consideration of one hundred and ninety chest injuries.—*Am. J. Surg.*, N. Y., 1921, xxxv, 221-223.

SHIPLEY, P. G., MCCOLLUM, E. V., SIMMONDS, NINA, and PARK, E. A.
Studies on experimental rickets. IV. Cod-liver oil as contrasted with butter fat in the protection against the effects of insufficient calcium in the diet.—*Proc. Soc. Exper. Biol. & Med.*, N. Y., 1920-21, xviii, 275-277.

SHIPLEY, P. G., PARK E. A., MCCOLLUM, E. V., and SIMMONDS, NINA.
Studies on experimental rickets. V. The production of rickets by means of a diet faulty in only two respects.—*Proc. Soc. Exper. Biol. & Med.*, N. Y., 1920-21, xviii, 277-280.

SHIPLEY, P. G., MCCOLLUM, E. V., SIMMONS, NINA, and PARK, E. A.
Studies in experimental rickets. VI. The effects on growing rats of diets deficient in calcium.—*Am. J. Hyg.*, Balt., 1921, i, 492-511.

SHIPLEY, P. G., PARK, E. A., MCCOLLUM, E. V., and SIMMONDS, NINA.
Studies on experimental rickets. VII. The relative effectiveness of cod-liver oil as contrasted with butter fat protecting the body against insufficient calcium in the presence of a normal phosphorus supply.—*Am. J. Hyg.*, Balt., 1921, i, 512-525.

SHOHL, A. T., and MASON, C. C.
Food at the front lines.—*Mil. Surgeon*, Wash., 1921, xlviii, 386-401.

SIEWERS, A. B.
Eye signs in intracranial tumors of the anterior fossa. With report of two cases.—*Arch. Neurol. & Psychiat.*, Chicago, 1921, vi, 424-428.

SIMON, C. E.
Giardia enterica: a parasitic intestinal flagellate of man.—*Am. J. Hyg.*, Balt., 1921, i, 440-491.

SISSON, W. R., and DENIS, W.
Studies on the inorganic constituents of milk.—*Am. J. Dis. Child.*, Chicago, 1921, xxi, 389-400.

SLACK, H. R.
Diseases of the tonsils, pharynx and nasopharynx. (Survey of literature from Sept. 1, 1920, to March 1, 1921.)—*In:* Nelson Loose-Leaf Med., 1921, ii, 18-19.

SLEMONS, J. M.
The prospective mother. A handbook during pregnancy. 2d. ed. New York, 1921. D. Appleton & Co., 343 p. 12°.

SMITH, W. H.
Address to the graduating class. Training School for Nurses, Peter Bent Brigham Hospital.—*Boston M. & S. J.*, 1921, clxxxiv, 367-371.
Adequate medical service for a community. Some factors of importance.—*J. Am. M. Ass.*, Chicago, 1921, lxxvi, 1055-1062.

STEINER, W. R.
Diseases of the muscles.—*In:* Oxford Med., 1921, iv, 353-366.

STEVENS, R.
A procedure for the cure of prostatic abscess.—*Tr. Am. Urol. Ass.*, 1920, Balt., 1921, xii, 19-24.

STONE, H. B.
The toxic agents developed in the course of acute intestinal obstruction, and their action.—*Surg., Gynec. & Obst.*, Chicago, 1921, xxxii, 415-419.

STRONG, R. P.
Trench fever.—*In:* Oxford Med., 1921, v, 423-437.
Remarks made at the closing session of the Inter-Allied Sanitary Commission, Paris.—*Boston M. & S. J.*, 1921, clxxxiv, 27-31.
International public health problems.—*North Am. Rev.*, Concord, N. H., 1921, ccxiii, 319-332.

STRONG, R. P., and COUNCILMAN, W. T.
Plague-like infections in rodents.—*Tr. Ass. Am. Physicians*, 1921, xxxvi.

STROUSE, S.
Dietetic therapeutics.—*Med. Clin. N. Am.*, Phila., 1921, v, 229-244.

SWARTZ, E. O., and DAVIS, D. M.
Action of mercurochrome—220 on the gonococcus.—*J. Am. M. Ass.*, Chicago, 1921, lxxvi, 844-846.
The action on the gonococcus of various drugs commonly used in the prophylaxis and treatment of gonorrhea.—*J. Urol.*, Balt., 1921, v, 235-253.

SWARTZ, E. O., YOUNG, H. H., and WHITE, E. G.
Further clinical studies on the use of mercurochrome—as a general germicide.—*J. Urol.*, Balt., 1921, v, 353-388.

TAYLOR, A. S.
The use of fine silk in surgery.—*China M. J.*, Shanghai, 1921, xxxv, 467-472.

THOMAS, H. M., JR.
Recurrent type 1 pneumonia: serum treatment of two attacks one month apart.—*Am. J. M. Sc.*, Phila., 1921, clxi, 103-109.

TIBBETTS, M. H.
Some essential points in the treatment of infantile paralysis.—*Minnesota Med.*, St. Paul, 1921, iv, 484-487.

TISDALL, F. F., and KRAMER, B.
A clinical method for the quantitative determination of potassium in small amounts of serum.—*J. Biol. Chem.*, Balt., 1921, xlvi, 339-349.
Simple method for the direct quantitative determination of sodium in small amounts of serum.—*J. Biol. Chem.*, Balt., 1921, xlvi, 467-473.
A simple technique for the determination of calcium and magnesium in small amounts of serum.—*J. Biol. Chem.*, Balt., 1921, xlvii, 475-481.
Methods for the direct quantitative determination of sodium, potassium, calcium, and magnesium in urine and stools.—*J. Biol. Chem.*, Balt., 1921, xlviii, 1-12.
The direct quantitative determination of sodium, potassium, calcium, and magnesium in small amounts of blood.—*J. Biol. Chem.*, Balt., 1921, xlviii, 223-232.

TISDALL, F. F., KRAMER, B., and HOWLAND, J.
Observations on infantile tetany.—*Am. J. Dis. Child.*, Chicago, 1921, xxii, 431-437.
The clinical significance of calcium concentration in the serum of children and possible errors in its determination.—*Am. J. Dis. Child.*, Chicago, 1921, xxii, 560-564.
The concentration of sodium and potassium as compared with that of calcium and magnesium in the serum of patients with active infantile tetany.—*Proc. Soc. Exper.* Biol. & Med., N. Y., 1921, xviii, 252-253.

TRUEBLOOD, D. V.
Fracture of the carpal scaphoid.—*Northwest Med.*, Seattle, xx, 277-279.

VANDERHOOF, D.
The significance of vertigo.—*South. M. J.*, Birming., Ala., 1921, xiv, 182-186.
The electrocardiograph in diagnosis.—*Virginia M. Month.*, Richmond, 1921, xlviii, 212-214. *Also: South. M. & S.*, Chattanooga, 1921, lxxxiii, 428-430.

VOEGTLIN, C., HOOPER, C. W., and JOHNSON, J. M.
Trinitrotoluene poisoning, its nature, diagnosis, and prevention.—*J. Indust. Hyg.*, Boston, 1921-22, iii, 239-254; 280-292.

VOEGTLIN, C., and SMITH, H. W.
Quantitative studies in chemotherapy. IV. The relative therapeutic value of arsphenamine and neoarsphenamine of different manufacture.—*J. Pharmacol. & Exper. Therap.*, Balt., 1920-21, xvi, 449-461.
Quantitative studies in chemotherapy. V. Intravenous versus intramuscular administration of arsphenamin; curative power and minimum effective dose.—*J. Pharmacol. & Exper. Therap.*, Balt., 1921, xvii, 357.

VOEGTLIN, C., SMITH, M. I., and JOHNSON, J. M.
Therapeutic value of chaulmoogra oil and its derivatives in experimental tuberculosis.—*J. Am. M. Ass.*, Chicago, 1921, lxxvii, 1017-1020.

WALKER, G.
Symphysiotomy as an aid to the removal of cancer of the prostate. A proposed new operation.—*Ann. Surg.*, Phila., 1921, lxxiii, 609.
The secretory pressure of the kidney as an index of pathologic conditions (Preliminary report). *Ann. Surg.*, Phila., 1921, lxxiii, 610-612.
Apparatus to aid in differentiation between an obstruction in the urinary outlet and paralysis of the bladder.—*J. Am. M. Ass.*, Chicago, 1921, lxxvii, 286-287.
A proposed standard treatment of early syphilis.—*South. M. J.*, Birmingham, Ala., 1921, xiv, 683-684.

WARFIELD, L. M.
Clinic of Louis M. Warfield, M. D., Milwaukee Hospital.—*Wisconsin M. J.*, Milwaukee, 1920-21, xix, 541-545.
The use of stimulants in pneumonia.—*Wisconsin M. J.*, Milwaukee, 1921-22, xx, 1-4.
Clinic of Dr. L. M. Warfield at Milwaukee County Hospital.—*Wisconsin M. J.*, Milwaukee, 1921-22, xx, 242-244.

WATERS, C. A., and BAETJER, F. H.
Injuries and diseases of the bones and joints; their differential diagnosis by means of the Roentgen rays. N. Y., 1921, P. B. Hoeber. 349 p. 4°.

WATERS, C. A., and YOUNG, H. H.
Pyelography.—*Soc. Internat. d'Urologie*, Paris, Juillet, 5-7, 1921.

WATKINS, S. S.
Indications for removal of the faucial tonsils.—*Kentucky M. J.*, Louisville, 1921, xix, 65-67.
Fifty-cent piece in the esophagus for three months, removal through mouth.—*Kentucky M. J.*, Louisville, 1921, xix, 523-524.
Symptoms, diagnosis and treatment of inflammatory lesions of the nasal accessory sinuses—from the viewpoint of the general physician and surgeon.—*Kentucky M. J.*, Louisville, 1921, xix, 682-688.
Primary scleroma of the larynx in a negro born in Maryland—*Surg., Gynec. & Obst.*, Chicago, 1921, xxxiii, 47-52.

WATTS, S. H.
Traumatic chylothorax.—*Ann. Surg.*, Phila., 1921, lxxiv, 691-696.

WEBSTER, L. T.
Lymphosarcoma. Lymphatic leukæmia. Leucosarcoma. Hodgkin's disease.—*Johns Hopkins Hosp. Rep.*, Balt., 1921, xx, 251-314.

WEBSTER, L. T., and LEWIS, W. H.
Migration of lymphocytes in plasma cultures of human lymph nodes.—*J. Exper. M.*, Balt., 1921, xxxiii, 261-269.
Giant cells in cultures from human lymph nodes.—*J. Exper. M.*, Balt., 1921, xxxiii, 349-360.
Wandering cells, endothelial cells, and fibroblasts in cultures from human lymph nodes.—*J. Exper. M.*, Balt., 1921, xxxiv, 397-406.

WEED, L. H., and HUGHSON, W.
The skull as a closed box (Proceedings).—*Anat. Record*, Phila., 1921, xxi, 88.

WELCH, W. H.
Introduction [to American Jour. of Hygiene].—*Am. J. Hygiene*, Balt., 1921, i, pp. iii-iv.
The place of Dr. Meltzer in American medicine.—*Proc. Soc. Exper. Biol. & Med.*, N. Y., 1920-21, xviii, 37-42. Memorial Number for S. J. Meltzer.

WESSON, M. B., and YOUNG, H. H.
The anatomy and surgery of the trigon.—*Arch. Surg.*, Chicago, 1921, iii, 1-37.

WHARTON, L. R.
Pelvic abscess, A study based on a series of seven hundred and sixteen cases.—*Arch. Surg.*, Chicago, 1921, ii, 246-314.
Rare tumors of the cervix of the uterus of inflammatory origin, condyloma and granuloma.—*Surg. Gynec. & Obst.*, Chicago, 1921, xxxiii, 145-153.

WHIPPLE, G. H.
Value of animal experimentation to mankind.—*Am. J. Pub. Health*, N. Y., 1921, xi, 105-107.

WHIPPLE, G. H., and DAVIS, N. C.
1. Liver regeneration following chloroform injury as influenced by the feeding of casein or gelatin.—*Arch. Int. Med.*, Chicago, 1921, xxvii, 679-687.

WHIPPLE, G. H., and DELPRAT, G. D.
Studies of liver function. Benzoate administration and hippuric acid synthesis.—*J. Biol. Chem.*, Balt., 1921-22, xlix, 229-246.

WHIPPLE, G. H., and ROBSCHEIT, F. S.
Iron and arsenic as influencing blood regeneration following simple anemia.—*Arch. Int. Med.*, Chicago, 1921, xxvii, 591-603.

WHITE, E. C., YOUNG, H. H., and SWARTZ, E. O.
Further clinical studies on the use of mercurochrome—as a general germicide.—*J. Urol.*, Balt., 1921, v, 353-388.

WIEL, H. I.
Truer standards in the diagnosis of heart failure. A hitherto unemphasized form of pulse irregularity.—*J. Am. M. Ass.*, Chicago, 1921, lxxvii, 749-753.

WIGHT, O. B.
Practical medical publicity.—*Proc. Alumni Assoc. Med. School, Univ. Oregon*, 1921, 9th Ann. Meeting.

WILLIAMS, J. W.
Report on graduate instruction in obstetrics and gynecology.—*Am. Med. Ass. Bull.*, Chicago, 1921, xv, 52-56.
Report on undergraduate teaching of obstetrics and gynecology.—*Am. Med. Ass. Bull.*, Chicago, 1921, xv, 146-152.
The problem of effecting sterilization in association with various obstetrical procedures.—*Am. J. Obst. & Gynec.*, St. Louis, 1921, i, 783-793.
Obstetrics and the general practitioner.—*Penn. M. J.*, 1920-21, xxiv, 290-296.
Twenty-one years' experience with Cæsarean section.—*Med. Standard*, Chicago, 1921, xliv, 14-24.

WILLIS, H. S.
Studies on tuberculous infection. VIII. Spontaneous pneumokoniosis in the guinea-pig. (Introduction by A. K. Krause.)—*Am. Rev. Tubercs.*, Balt., 1921-22, v, 189-217.

WISLOCKI, G. B., and PUTNAM, T. J.
Absorption from ventricles in experimentally produced internal hydrocephalus.—*Am. J. Anat.*, Phila., 1921, xxix, 313.

WOODS, A. C.
Immune reactions following injuries to the uveal tract.—*J. Am. M. Ass.*, Chicago, 1921, lxxvii, 1317-1322.

WOOLLEY, P. G.
Blood sugar tolerance in cancer and in hypertension. (Editorial.)—*J. Lab. & Clin. M.*, St. Louis, 1920-21, vi, 227-229.
Complications of the arsphenamine treatment of syphilis. (Editorial.)—*J. Lab. & Clin. M.*, St. Louis, 1920-21, vi, 344-347.
Syphilology and clinical synthesis. (Editorial.)—*J. Lab. & Clin. M.*, St. Louis, 1920-21, vi, 469-471.
Superinfection in syphilis in its relation to subtreatment. (Editorial.)—*J. Lab. & Clin. M.*, St. Louis, 1920-21, vi, 717-719.

WRIGHT, C. B.
Duodenal ulcer: medical treatment in ambulant cases.—*Journal-Lancet*, Minneapolis, Minn., 1921, xli, 396-397.

YATES, J. L.
An outline of twelve years' study of Hodgkin's disease and allied affections.—*Wisconsin M. J.*, Milwaukee, 1920-21, xix, 447-451.

YOUNG, C. W., and HAN, C. H.
Agglutination titer following repeated intravenous injections of tab vaccine.—*China M. J.*, Shanghai, 1921, xxxv, 400-404.

YOUNG, H. H.
Surgery of the prostate.—*In:* Surgery, Its Principles & Practice (Keen). Phila. & Lond., 1921, viii, 530-607.
The value of drugs in urology.—*J. Am. M. Ass.*, Chicago, 1921, lxvii, 1327-1332.
Success of the campaign for combating venereal disease in the A. E. F.—*Mil. Surgeon*, Wash., 1921, xlviii, 213-222.
Demonstration of a new combined cystoscopic and X-ray table.—*Tr. Am. Urol. Ass.*, 1920, Balt., 1921, xii, 344-347. *Also: J. Urol.*, Balt., 1921, v, 391-404.

YOUNG, H. H., and CASH, J. R.
A case of pseudohermaphrodismus masculinus, showing hypospadias, greatly enlarged utricle, abdominal testis and absence of seminal vesicles.—*J. Urol.*, Balt., 1921, v, 405-430.

YOUNG, H. H., and WATERS, C. A.
Pyelography.—*Rapport de la Soc. Internat. d'Urologie*, Paris, Juillet 5-7, 1921.

YOUNG, H. H., and WESSON, M. B.
The anatomy and surgery of the trigon.—*Arch. Surg.*, Chicago, 1921, iii, 1-37.

YOUNG, H. H., WHITE, E. C., and SWARTZ, E. O.
Further clinical studies on the use of mercurochrome—as a general germicide.—*J. Urol.*, Balt., 1921, v, 353-388.

ZIMMERMANN, E. L.
A comparative study of syphilis in whites and in negroes.—*Arch. Dermatol. & Syph.*, Chicago, 1921, iv, 75-88.
Syphilitic iritis, its racial incidence and its association with secondary syphilis and with neurosyphilis.—*J. Am. M. Ass.*, Chicago, 1921, lxxvi, 1818-1819.

RECEIVED TOO LATE FOR INSERTION IN ALPHABETICAL ORDER

BERRY, J. M., and HOWARD, W. P.
Reports from the Roentgen-ray laboratory of the Albany Hospital.—*Albany M. Ann.*, 1921, xlii, 368-376.

BURROWS, M. T.
Problems in cancer research.—*J. Cancer Research*, Balt., 1921, vi, 131-138.

DICKSON, E. C., and BURKE, GEORGINA S.
Botulism. A method for determining the thermal death time of the spores of *Bacillus botulinus*.—*Proc. Soc. Exper. Biol. & Med.*, N. Y., 1921-22, xix, 99-101.

DIEUAIDE, F. R., and DAVIDSON, E. C.
Terminal cardiac arrhythmias. Report of three cases.—*Arch. Int. Med.*, Chicago, 1921, xxviii, 663-677.

HALSTED, W. S.
Ligations of the left subclavian artery in its first portion.—*Johns Hopkins Hosp. Rep.*, Balt., 1921, xxi, 1-96.

HIGGINS, W. H.
Certain types of cerebral manifestations in cardio-renal diseases.—*Virginia M. Month.*, Richmond, 1920-21, xlvii, 598-601.

LEVY, R. L.
Alterations in the cardiac mechanism after administration of quinidine to patients with auricular fibrillation.—*Proc. Soc. Exper. Biol. & Med.*, N. Y., 1921-22, xix, 88-91.

MACHT, D. I.
Isopropyl alcohol, a convenient laboratory anesthetic for cats.—*Proc. Soc. Exper. Biol. & Med.*, N. Y., 1921-22, xix, 85.

PEARL, R.
The vitality of the peoples of America.—*Am. J. Hyg.*, Balt., 1921, i, 592-674.

PARFITT, C. D.
The care and employment of the tuberculous ex-service man after discharge from the sanatorium.—Ottawa, 1921, F. A. Acland, 77 p. 8°.

ROBINSON, G. C.
Organization of the medical clinic of The Johns Hopkins Hospital.—*Johns Hopkins Nurses Alumnae Mag.*, Balt., 1921, xx, 226-227.

SCHLAEPFER, K.
Die Carrel-Dakin-Behandlung infizierter Wunden.—*München. med. Wchnschr.*, 1921, lxviii, 1490-1492.

TISDALL, F. F.
The etiology of rickets.—*Canad. M. Ass. J.*, Toronto, 1921, xi, 934-943.

WEBSTER, L. T.
Experiments with *B. enteritidis* (*murium*) on normal and immune mice.—*Proc. Soc. Exper. Biol. & Med.*, N. Y., 1921-22, xix, 71-72.

PUBLICATIONS

The following twelve monographs:

Benzol as a Leucotoxin. By LAURENCE SELLING, M. D. 60 pages. Price, $1.00.

Primary Carcinoma of the Liver. By M. C. WINTERNITZ, M. D. 42 pages. Price 75 cents.

The Statistical Experience Data of The Johns Hopkins Hospital, Baltimore, Md., 1892-1911. By FREDERICK L. HOFFMAN, LL.D., F.S.S. 161 pages. Price, $2.00.

Venous Thrombosis During Myocardial Insufficiency. By FRANK J. SLADEN, M. D., and MILTON C. WINTERNITZ, M. D. Price, 75 cents.

The Origin and Development of the Lymphatic System. By FLORENCE R. SABIN. 94 pages. Price, $2.00.

Leukaemia of the Fowl: Spontaneous and Experimental. By HARRY C. SCHMEISSER, M. D. Price, $2.00.

The Structure of the Normal Fibers of Purkinje in the Adult Human Heart and Their Pathological Alteration in Syphilitic Myocarditis. By O. VAN DER STRICHT and T. WINGATE TODD. Price, $2.00.

The Operative Story of Goitre. The Author's Operation. By WILLIAM S. HALSTED, M. D. Price, $3.50.

Study of Arterio-Venous Fistula with an Analysis of 447 Cases. By CURLE L. CALLANDER, M. D. Price, $2.50.

Ligations of the Left Subclavian Artery in its First Portion. By WILLIAM S. HALSTED. Price, $2.00.

The Pathology of the Pneumonia in the United States Army Camps During the Winter of 1917-18. By WILLIAM G. MACCALLUM. Price, $1.50.

Pathological Anatomy of Pneumonia Associated with Influenza. By WILLIAM G. MACCALLUM. Price, $1.50. (This monograph will be on sale within a short time.)

are now on sale by THE JOHN'S HOPKINS PRESS, Baltimore. Other monographs will appear from time to time.

The Johns Hopkins Hospital Bulletins are issued monthly. They are printed by the LORD BALTIMORE PRESS, Baltimore. Subscriptions, $4.00 a year (foreign postage, 50 cents), may be addressed to the publishers, THE JOHNS HOPKINS PRESS, BALTIMORE; single copies will be sent by mail for fifty cents each.